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What Future for the European Community?

THE enlargement of the European Community that will take place next week will make a mark in history. Not even the British Labour Party, sulking in its tent and refusing to send representatives to the European Parliament, will dissent from that. For although there is no doubt that the six countries now in the European Community would by themselves evolve into a strong political and economic force, the accession of Britain, Denmark and Ireland will accelerate the process. For one thing, the increase of scale now in prospect will increase the momentum towards cohesion. Then there is every prospect that the British influence will be much more powerful than would be suspected from the past two decades of vacillation and from the divisions which remain in British public opinion. As things have turned out, the most compelling reasons for British membership of the European Community are political, not economic, and this change of emphasis since negotiations for membership first began will determine the way in which the British delegation functions in Brussels. With any luck, the British influence will be subversive in the sense that Edmund Burke would have approved of, for there is likely now to be much more concern with the removal of impediments to European integration than with the further elaboration of the bureaucracy in Brussels.

Bureaucracy as such is not, of course, a scandal. Nations of all kinds find a civil service necessary. The complaint against the bureaucracy in Brussels is chiefly that there is only the most imperfect machinery for determining the political effects of what appear to be administrative decisions. The Council of Ministers is necessarily a hot-house of a talking shop. The permanent representatives of member nations in Brussels, the commissioners, function as if they were hybrids between cabinet ministers in an incomplete government of Europe and ambassadors who pursue national interests. And for all the protestations of good faith at the Paris summit in November, nobody can really tell what influence the European Parliament will have on the decisions made in Brussels. In due course, these anomalies will have to be ironed out. A formal constitution and some means of electing people to the European Parliament will be necessary, as the Dutch were clear-headed enough to recognize in November. It is hard to think that all this will be done by 1980, the goal specified in the summit communiqué, but even these thorny questions may be simplified by the growth of regionalism within the member nations. After all, it will not be long before some British Government recognizes that the problem of Ulster might be diminished if Ulster were directly represented in some supra-national parliament.

More immediate objectives will, however, necessarily dominate the next few years, and there are several obvious ways in which the new members of the community can and should take up the cudgels. As it happens, many of the steps which need to be taken quickly are closely connected with the administration of education, research and

development in Europe. The opportunities in education, especially higher education, typify the way in which agreements between governments could quickly benefit the European cause. As things are, European universities are closely controlled by national governments. In many countries, France for example, university teachers are government employees. The result is that the exchange of teachers and even students between different institutions is not nearly as fruitful as it should be. It cannot be very long, however, before these artificial impediments to the free movement of people are seen to be absurd. The immediate need is that university systems should be disestablished at least to the point at which universities as independent corporate institutions are free to employ whoever they choose as teachers. And although it is inevitable that governments will continue to be responsible for the cost of educating their students, there is a strong case for asking that students should be able to follow courses at universities outside the countries in which they happen to have been born. What this requires is an understanding between governments that migrations of this kind are desirable and some method of making sure that costs are equitably apportioned. On research, which may be properly regarded as a necessary part of the cost of operating universities, it is again most probable that universities will continue to be supplied with grants from predominantly national resources, but there is a case for a modest start on the European Science Foundation which the European Commission has been fostering, if only so as to provide a forum within which the grant-giving bodies can evolve some common policy.

Economically much more important are the steps which can and should be taken quickly to rationalize the policies of European governments on public purchasing. For all the pretence which there has been that the European Community is a common market, the fact remains that national governments deliberately tend to rely on their traditional suppliers when buying capital equipment of all kinds—typewriters and telephone equipment as well as computers and military supplies. To the extent that government departments and nationalized industries are necessarily a growing source of business of this kind, their backward practices take the edge off the advantage of free competition which is supposed to sustain and make rational the European Community. Given the relationship between Brussels and national governments, however, there is little the European Commission can do to change this paradoxical state of affairs. It is, however, urgently necessary that there should be a change. Although the British Government has as much reason as any other to fear that more liberal purchasing policies would bring trouble, it shares with Germany and the Low Countries the temperament to take the risk.

Defence is another field in which there should be a rapid erosion of chauvinism, and in which the British Government is well placed to take the lead. A year or two from now, if not already, it will be absurd to think

that the defence of Europe (whatever that may mean) can be best assured by supposing that governments can independently decide what contributions they can afford to make to NATO (from which, in any case, France has chosen to be excluded). It is a step in the right direction, but not far enough, that the European members of NATO (with Norway, Greece and Turkey included) should have declared their intention to pursue common purchasing policies on the eve of the NATO ministerial meeting earlier this month. The truth is, however, that circumstances require nothing much less than a revival of the concept of a European Defence Community, the King Charles's head of the 1950s. To coordinate plans is less important than to make common plans. The way in which the French Minister of Defence, Mr M. Debré, has been proclaiming in the past few weeks the need that France should forever remain independent in defence is not to be taken too seriously, for much can change in the months ahead, with the imminence of the French elections, the European negotiations on Mutual Balanced Force Reductions and the European Security Conference. Given the inevitable diffidence of Germany, however, it falls to the British Government to make the first approaches. They should not be long delayed.

In these and many other fields in which there are opportunities for old-fashioned methods for the removal of impediments to integration, the guiding principle should be that the strength of Europe lies not merely in the scale of the political unit now being fashioned but in the way in which the different member nations can complement each other's strengths and weaknesses. In the nature of things, the horse-trading at Brussels works in favour of similarity and fair shares, not diversity. This is yet another reason why the bureaucracy in Brussels must sooner or later be turned into an instrument for reconciling essentially political agreement between states still far too anxious to ensure that their material benefits from the European Community are greater than their material contributions to it. The change will take time, but there is not much time to lose.

Docksey Unveiled

THE Select Committee on Science and Technology has cheekily found a way of giving public circulation to the report by Mr P. Docksey on the British Government's role in the exploitation of inventions (see page 517). By all appearances, the committee has found a neat way of gratifying its own wish to persuade the government to a more open policy on the publication of documents: a document has been handed over, there is nothing but the committee's inclinations or disinclinations to prevent full publication. All this is reasonable enough, for there is no way in which the government can tell the House of Commons what to do (even if it is able to tell the members of its own political party which way to vote). It is to be hoped that Mr Airey Neave and his colleagues will now make a set at the many other documents crucial to the administration of science and technology—not merely the Vintner Report on nuclear energy but the contract documents between the research councils and the government departments soon to become their customers, for example—which the government is likely to wish to sit on.

The affair of the Docksey Report remains a minor mystery. The government has steadfastly refused publication on the grounds that Mr Docksey's views on the exploitation of inventions were intended for internal consumption. Mr Docksey himself told the Select Committee earlier this year that he could see no reason why publication should be denied. The outcome has been to create the impression that Mr Docksey had trenchant criticism to make of the organization of the National Research Development Corporation, and that his recommendations were for some reason or other unacceptable to the government. The truth is, however, that the report itself is an innocuous document which is but a pale echo of the many cogent criticisms which have and might be made of the NRDC. Its analysis is weak and its recommendations ill-founded. If anybody is embarrassed by publication, it will be Mr Docksey himself.

NRDC is a little like Topsy. When it began, in 1949, the objective was clear enough. Rightly or wrongly, the government then held that a great many inventions of potential importance to industry were not being exploited with sufficient skill and vigour, with the result that some of the benefits of even publicly supported research were being lost to industrial enterprises overseas. Blessed as it was with royalties from the exploitation of the Bailey Bridge, the corporation set about exploiting inventions it could lay its hands on from all kinds of sources—government laboratories, universities and private inventors. By the early 1960s, the corporation persuaded itself and the Treasury that there are also many circumstances in which industrial companies are unable fully to exploit inventions which they make themselves, with the result that it became a kind of merchant bank, backing innovations with development funds in return for a royalty on sales or even a shareholding in the common enterprise. Throughout this period, there has been continuing uncertainty about the fiscal basis of the corporation's business. Except for a short period in the 1960s, the corporation has been expected to balance its books, using the income from proved and profitable investment to sustain the cost of new investments. Although the corporation has recently been doing much to ingratiate itself with the government accountants, the potential hazards of some of its more recent investments are alarming.

Unhappily, Mr Docksey has very little to say about the overall effectiveness of the NRDC in the two decades of its operations. And here, of course, the test is not whether the corporation has managed to balance its books but whether the inventions which it has backed with public funds have justified its own belief in them and the expectation that Britain is the home of unrequited invention. In other words, Mr Docksey's report should have included an analysis of the business generated by those of the NRDC's projects which have turned out well, and an attempt to describe how the corporation's judgment has improved with time, based possibly on an analysis of successful and unsuccessful projects. In the nature of things, not every invention can be the starting point for a successful programme of development, but if the marginal investments are too chancy, there is obviously a point at which the government had better abandon any attempt to rescue the possible successes. Most probably, the NRDC has an honourable tale to tell. The questions that Mr Docksey should have answered are whether there is a continuing job for the government to do in the exploita-

tion of inventions that nobody else will look at, what arrangements there should be for channelling hopeful inventions within the public sector towards industry and then, quite separately, what arrangements should be set up within the Department of Trade and Industry for sponsoring industrial development—a question now in part at least answered by the setting up of the department's requirements boards.

In the event, Mr Docksey's proposals for change are hopelessly too formal. In his view, there should be a Development Council within the Department of Trade and Industry, with responsibility for overseeing the work of the NRDC and of another similar organization (to be established) but working exclusively with inventions produced within the government's own industrial research establishments. An essential part of the proposal is that the NRDC and its putative twin should be concerned only to demonstrate that an invention is potentially profitable. It would then be for the Development Council to make arrangements, usually in partnership with industry, to sponsor the further stage of development needed to turn the invention into a new product or process. The scheme has the merit of tidiness, and it is sensible to suggest that the NRDC should be dissuaded from the kinds of direct involvement in industrial enterprises typified by its work with hovertrains, but there are few other benefits in the arrangement.

Open Purse?

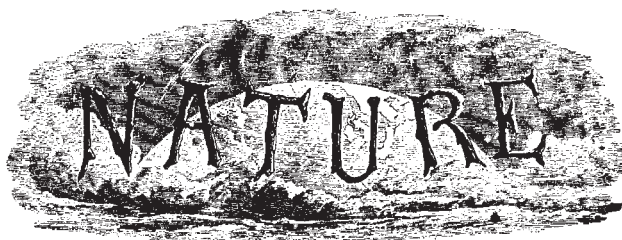
ONE way and another, the prospect for the British science budget is coming to seem increasingly bleak. So much can be told from the latest estimate of public expenditure in the next five years (*Public Expenditure to 1976-77*, Cmnd 5178, HMSO, £0.68) in an otherwise glad-handed document which records increases of public expenditure of £700 million in the current financial year (or 2.5 per cent) and £1,250 million in each of the two succeeding years. The total expenditure of the research councils, for example, is expected to rise from £137.7 million in the current year to £149 million in 1975-76, which sum includes the £27 million which will be then carried on the budgets of individual departments and which will be spent with the research councils only if those new-found customers decide that that is how it should be spent. Between 1975-76 and 1976-77, the science budget (exclusive of work commissioned by the departments) is reckoned to increase from £122 million to £126 million (at 1972 prices) or by 3 per cent. By any test, these estimates are gloomy.

The first thing to be acknowledged is that the budgets now proposed are probably too small to sustain the kind of work on which the councils are already engaged. In the next five years, the disposable income of the research councils will increase by £15 million, or by 13.5 per cent. (The White Paper, rapidly being converted into the next best thing to a forward economic plan, makes an intelligent distinction between costs at constant prices and those likely to emerge in practice, on account of the differential consequences of inflation for public and private expenditure.) Much of this extra money is, however, already bespoken. If, for example, the research councils are required to support a large proportion of the extra 7,000

postgraduate students at British universities five years from now, the cost could be between £3 million and £5 million a year. Then the contribution of the Science Research Council to projects in nuclear physics is certain to increase in the years immediately ahead, even if the rising cost of contributions to the 300 GeV accelerator is offset by economies at other accelerators. The budget of the Social Science Research Council is also likely to continue to increase by 10 per cent or so a year, which could mean an extra £3 million five years from now. On the face of things, the research councils will find themselves spreading substantially the same amount of money as at present over a substantially larger number of grant applications, especially if the burgeoning polytechnics become consumers on a more substantial scale.

This is why the government should be forced to answer at least one awkward question. The justification for the large increase of public expenditure in the next two years is the Keynesian argument (for even conservative governments are Keynesian now) that it is necessary to compensate for the present trough in the trade cycle. But is not spending on research and development as good a Keynesian remedy for recession as subsidies for the coal industry and the railways? Indeed, an increase of the science budget is on the face of things the kind of investment that could contribute enormously to the economy when the recession (if that is the name for the present despondency of British industry) is over. In short, the long-term decision which has been taken on research is unwise, not merely harsh.

100 Years Ago



Pollen-eaters

FROM a note in *NATURE*, Dec. 19, it appears that it has hitherto been a mooted question among entomologists whether any species of Diptera are pollen-eaters. I have often watched certain slender-bodied flies, belonging to or allied to the family of Noverers (*Syrphidae*), in the act of feeding on the pollen of various flowers, which they effected by a quick jerking and grinding movement of the mandibulae. I once witnessed the exhibition of a much more surprising taste by one of these insects, which, together with a small yellow ant, I watched for a considerable time feasting on a gout of resinous matter that had exuded from a wound in the bark of a spruce fir-tree.

Mention of ants reminds me of Mr. Meldola's statement (*NATURE*, vol. vi. p. 279) that Dr. Bree has pronounced their aphid-milking instinct a myth. While an undergraduate at Cambridge, I have more than once been a pleased spectator of this mythical performance; but Dr. Bree's incredulity may be explained by the fact that all ants have not this instinct. At least, though for many years constantly on the look-out for it, only one instance of it has come under my notice on this side of the Channel. On one occasion when I introduced an ant among a number of aphides, her first act was to seize one of them in her jaws; but after carrying it for a short distance over the backs of its fellows, she released it, and made what haste she could out of the company of creatures whose polite attentions she seemed by no means to appreciate.

Kilderry, Co. Donegal

W. E. HART

From *Nature*, 7, 161, January 2, 1873.

OLD WORLD

European Space Agency by 1974

EUROPE is to have its own space agency by 1974. At a meeting of the European Space Conference in Brussels last week the twelve ministers of the member states agreed that a new organization, to be known as the European Space Agency, should be formed out of the European Launcher Development Organization and the European Space Research Organization, if possible in 1974.

After a lengthy meeting, the start of which was delayed when Mr Michael Heseltine, Minister for Aerospace and Shipping, was held up by fog, the European ministers emerged with a framework which they believe will give Europe a real chance to make progress in space. The conference agreed that the agency's aim will be to integrate the national space programmes in a single European space programme, "as far 'and as fast as is reasonably possible", and the conference also gave general approval for the post-Apollo sortie laboratory project and the French launcher plans (see *Nature*, 240, 434; 1972) to be carried out and managed within a common European framework. But the conference put aside the questions of who is to participate in these projects and who is to finance them. Discussion of these will come later. Mr Heseltine made it plain, however, that Britain's attitude to a European launcher has not changed. Britain is still happy with assurances from the United States that launchers will be made available and still sees the creation of a European launcher as an unnecessary effort. Britain, therefore, will not be contributing to the launcher, although it emerged at the conference that West Germany may be interested in the new French proposals which involve the scrapping of Europa III. The ESC also agreed that there should be a rationalization of the various satellite programmes that Europe is currently financing, including the GTS programme, on the understanding that the agreement made by ESRO in 1971 is not being questioned. This agreement includes plans for a prototype telecommunications satellite to be put into orbit by a launcher obtained from the United States.

The hard details of the agency have still to be worked out, but the principle is clearly established that financial contributions to its work will be based upon each country deciding which projects it wants to support and not upon a levy based on the gross national product of each country—the traditional

way of funding international agencies.

It is not intended that all national programmes will be immediately handed over to the agency, but that programmes should gradually be phased in over the years. Not all Britain's space activities will be affected. British commitments to Intelsat and the Ministry of Defence's Skynet project will not be involved.

Before going to Brussels, Mr Heseltine gave evidence to the Select Committee on Science and Technology and gave the government's answer to the committee's proposals in its fifth report (published in November 1971) that Britain should create a National Space Agency. Mr Heseltine explained that if a European agency was formed following the Brussels meeting a British agency would be outmoded.

Discussing the financing of Britain's space programme Mr Heseltine said

ENERGY

Future of Coal

HARD on the heels of the government's decision to wipe off £475 million of the National Coal Board's debt (*Nature*, 240, 431; 1972), the British coal industry has come out with a document which argues that coal is an indispensable part of any future European energy plan.

In a remarkable display of unity, Mr Derek Ezra, chairman of the NCB, Mr Joe Gormley, president of the National Union of Miners, and representatives of other branches of the coal industry last week wholeheartedly supported the report, *Coal and Energy Policy in Europe*, which calls for coal to be used to "its full and effective potential" within the European Community.

Britain's entry into the EEC next week will increase the community's coal output from 170 million to 300 million tons, and the NCB in particular sees this as an appropriate time to try to increase Britain's coal exports to Europe from the present level of 3 million tons to 5 million.

But the nub of the report lies in the calculations of the combined future energy requirements of the initial six members of the EEC and Britain (see table). The balance between energy needs and energy supply has to be filled with coal or imported oil and "in view of all the difficulties envisaged for oil we consider that as large a part of this market as possible should be supplied with coal", says the report.

The report suggests that an energy

that "it is my specific view that we are not going to increase our spending on space". A European agency would only rationalize the current expenditure of the European nations and prevent needless duplication. "I am sure", he said, "that Europe will be brought together in time by economic pressures and in my view the sooner the better".

At the start of the European Space Conference, Mr Théo Lefevre, the Belgian Science Minister and chairman of the conference, appealed for some measure of unity in space policy. Europe, he said, had just six months to decide a course of action, the implication being that the United States is not prepared to wait any longer than that for a reply to its invitation to Europe to participate in the post-Apollo programme by building the sortie laboratory.

policy for the enlarged EEC should be based on the following points. First, that oil from the North Sea should be used to displace imported oil rather than other indigenous energy sources. Second, that natural gas should be conserved by restricting its use for premium purposes. Third, that nuclear power should be developed at the most economic rate, keeping its long-term potential in mind.

While entry to the EEC provides opportunities to the British coal industry, there is also the fear that entry will provide a gateway for coal which is at present being imported into the EEC from outside countries, usually with the help of massive subsidies from the governments concerned, to be sold in Britain at a lower cost than British coal. This coal is imported now under a quota system, and Mr Ezra said last week that once Britain was in the EEC he would try to get the community's policy on coal imports reviewed.

Combined Primary Energy Requirements of the Six and Britain

	Million tonnes coal equivalent		
	1970	1980 (est.)	1985 (est.)
Natural gas	89	285	355
North Sea oil (incl. Norway)	—	170	340
Lignite	33	38	37
Nuclear power	13	105	235
Hydro electricity	47	48	49
	182	646	1,016
Balance (coal and imported oil)	992	1,179	1,254
Total	1,174	1,825	2,270

SELECT COMMITTEE

Docksey Report Surfaces

THE government was sharply criticized last week by the Select Committee for Science and Technology. In its first report of the new session, the committee attacks the government's secretive approach to the advice it obtains and, for good measure, publishes the much-discussed inquiry into the National Research Development Corporation and other aspects of government-funded development and exploitation of inventions which Mr Patrick Docksey carried out for the Department of Trade and Industry. Mr John Davies, then Secretary of State for Trade and Industry, refused to publish the report earlier this year.

Mr Airey Neave, chairman of the select committee, said last week that he was concerned not so much with the contents of Mr Docksey's report as with the principle that the government appears willing to suppress a report simply because it disagrees with its conclusions. When Mr Davies gave evidence to the select committee in May 1972, he said that the government would perhaps not publish the Docksey report at all "if they were to reach the conclusion that it was incompatible with the government's broad approach to research and development".

The select committee strongly disagrees with this view. "Too often governments seek to avoid being questioned on aspects of policy by appointing an inquiry," the committee says, "then refusing to make any comment on the subject until the inquiry has reported. This advice becomes doubly objectionable if the government then decides not to publish the report."

The select committee's publication of the report brings to a head many months of disagreement between the committee and the Department of Trade and Industry. The Docksey report was widely reputed to be investigating among other things the future of the National Research Development Corporation. It was commissioned in 1971 from Mr Patrick Docksey, formerly general manager of BP's Research and Technical Development Department, who reported in December 1971. The select committee asked Mr Davies to publish the report in May, and in July took evidence from Mr Docksey after Mr Davies had refused publication. Mr Docksey said he saw no reason why the report should not be published, so the select committee, using its power "to send for persons, papers and records", requested that they be sent the report which they received in September.

Mr Neave, explaining that the select committee's action in publishing a report that the government has refused

to publish is without precedent, went on to say that "the practice has been established that the government does not publish anything if it can be avoided. What is essential for the future is that the select committee should not be obstructed with regard to documents that are the subject of their work". Mr Neave added that the select committee is to send for, and will consider publishing, the Vintner report on thermal reactors, another report that the government has suppressed.

The Docksey report itself, which Mr Neave rightly describes as an "unsensational document", recommends that a development council be set up to act as a decision and accounting centre for all government-funded development work on projects that have been proved feasible and had their commercial possibilities defined (other than projects developed specifically by a department for its own use), and to oversee the activities of NRDC. Exploitation of inventions should be managed by two groups, one, the NRDC, responsible for all government-funded civil inventions from the research councils, universities and government laboratories other than the Department of Trade and Industry establishments, and the other to cover the DTI establishments' activities.

The NRDC, Mr Docksey says, should continue to seek out inventions arising from the research councils and universities, but should use university industrial liaison groups and officers as its agents, rather than, in the first instance, exploring the possibilities itself.

ENVIRONMENT

Radioactive Levels

THE amount of radioactivity deposited by rainwater in Britain continues to decrease as it has done every year since the early 1960s. In the first six months of 1972 the amount of atmospheric activity deposited at several sites in Britain was only one half of that deposited a year earlier and a twentieth of that deposited during the early 1960s, according to the UK Atomic Energy Authority (*Radioactive Fallout in Air and Rain*, HMSO, £1).

Thirty-five per cent of the atmospheric activity in the early part of this year in Britain can be attributed to a Chinese nuclear weapon exploded on October 14, 1970, and ten per cent to a later Chinese explosion on March 18 of this year.

The estimated total amount of radioactive strontium-90 and caesium-137 deposited on the Earth as a result of atmospheric testing of nuclear weapons has been constant since about 1966. This stability is due to the fact that the 0.44 megacuries of radioactive caesium

and the 0.26 megacuries of radioactive strontium which has been the average amount deposited world-wide in the past five years merely replaces the amounts of these isotopes which have decayed during the year to stable isotopes.

The Harwell team also reports on the amounts of barium-140 found in the atmosphere soon after a nuclear explosion. During late 1971 and the first few months of 1972, barium-140 of half life 12.8 days was detected at stations throughout the world on three separate occasions. In late November and early December 1971, nuclear products of the Chinese explosion of November 18, 1971, were detected at Harwell. The isotope was next detected during the middle of January and its intensity in the atmosphere finally became too small to detect in early March. The third and largest concentration of barium-140 was detected at the end of March—products of the Chinese explosion of March 18.

METEOROLOGY

Pacific Typhoons?

from a Correspondent

THE Typhoon Committee of the Economic Commission for Asia and the Far East has now reviewed progress in the improvement of typhoon warning stations, communications and warning systems within Asia and the Far East. At the fifth annual meeting of the committee held in Bangkok during November, Hong Kong, Japan, Korea, the Philippines and Thailand welcomed the Khmer Republic (Cambodia) as a new member of the committee. Australia, France, Germany, the United States and the Soviet Union sent observers.

The United States reported at the meeting on the progress of the Storm Fury project, designed to decrease the intensity of typhoons by cloud seeding, supposed to induce rainfall and hence to decrease the intensity of a storm by broadening the area from which latent heat is released. The results of the experiments are so far inconclusive and effects which have been observed could not categorically be ascribed to seeding.

Efforts to reduce evaporation from the sea in the path of typhoons—the energy source of the storm—by spraying the sea with chemicals have also failed because of the rapid distortion of the chemical film by the violent turbulence at the sea surface.

So far, the Storm Fury project has been confined to the Atlantic in spite of the efforts of the ECAFE Typhoon Committee to transfer it to the Pacific where there are more storms each year to test the techniques. The project cannot now be transferred to the Pacific before 1975.

NEW WORLD

Physics and Social Responsibility

by our Washington Correspondent

THE American Physical Society, one of the most venerable of learned societies, has always managed to stay somewhat aloof from the messy world of ethics and politics. But, during the past year or so, it has been creaking a little under pressures applied by some of its younger members who want the society to concern itself with questions of social responsibility in science. The debate—if a mild stirring among a fraction of the society's members can be so called—has thrown up a whole series of questions about the role of a learned society such as the APS. It has also provided an object lesson in in-fighting in a large organization.

Spearheading the move for change is Robert H. March, a nuclear physicist from the University of Wisconsin, who won an APS prize last year for his book *Physics for Poets*. March headed a list of 276 petitioners who in October 1971 proposed an amendment to the society's constitution which would graft on to the present aims of the APS, which are simply "the advancement and diffusion of the knowledge of physics", the words "in order to contribute to the enhancement of the quality of life for all people. The society shall assist its members in the pursuit of these humane goals and it shall shun those activities which are judged to contribute harmfully to the welfare of mankind."

Few would disagree that the intention of the amendment is as laudable as God, motherhood and apple pie, but many have argued that it is unenforceable, that the wording is unpalatable and that the American Physical Society should steer clear of ethical questions and just concern itself with physics. The last part of the amendment, instructing the society to shun those activities judged to be harmful to mankind, has borne the brunt of the criticisms.

The March Amendment, as it has come to be known, provided something of a talking point at the spring meeting of the APS, and it was to have been put to a vote by mail ballot along with the voting for the president of the society. But, when the presidential ballots were sent out last month, no voting slips for the constitutional change were included, and it now seems unlikely that the amendment will be put to a vote until June 1973.

This is what happened. Faced with certain defeat, March and some of his

colleagues decided to delete the last part of their amendment, so that the society would not be forced to shun anything, but it would still be concerned with issues of social responsibility. But they were told by Dr William Havens, executive secretary of the society, that since the original amendment was proposed by petition, it could only be changed by petition. Alternatively, the council could expedite matters and put on a liberal face by proposing the modified March Amendment, and allow March then to withdraw his original version. The council was expecting March to come to its meeting in October to discuss what he wanted to do, but when he didn't turn up it decided to postpone the vote on the amendment.

March, meanwhile, is busy sounding out the opinions of his colleagues and is planning to attend the next council meeting which will be held at the end of January. But Havens pointed out last week that if there are any changes made to the amendment, they must be printed in the APS bulletin before ballots can be sent out—he reckons that the whole process could take up to six months.

Although March is annoyed by the council's legalistic attitude, he said that he is not disappointed at the delay because the longer the debate on the amendment continues, the more time he will have to "educate the members of the society about the need for the change". His chances of success will

undoubtedly be improved if he deletes the part of the amendment which requires the society to shun activities judged to be harmful to mankind, but he is still not optimistic about the outcome.

How will the proposed change affect the workings of the society? Dr Joseph E. Mayer, of the University of California, San Diego, who takes over the presidency next month, said that without the last part of the amendment, "I really don't see how it's going to change the role of the society itself", although he confessed that he is a little sceptical about the ability of physicists to tell in advance whether or not their work will be beneficial.

But the philosophical question underlying the amendment is basically fairly simple—should a learned society be concerned only with the development of science and remain ethically neutral about its applications, or does it have a duty at least to discuss questions of social responsibility and perhaps to take a stand against those applications which are clearly harmful?

March has no doubts about the answer. He wrote in the November issue of *Physics Today* that the move towards concentrating sources of support for science in the hands of the government and large institutions has increased the need for the APS to take an ethical stand. "Much of our research is funded to implement specific policy goals", he wrote, "and many of

CREATION

Fundamental Changes

THOSE who believe that a literal interpretation of the Book of Genesis offers the best explanation of the origins of man won a remarkable, if partial, victory in the state of California last week. They managed to persuade the California State Board of Education to adopt a requirement that school biology textbooks used in the state should severely qualify all statements about evolution, relegating them to theory and not fact. The effect will be to amend statements such as "the Earth was formed with the rest of the solar system many years ago" to "many scientists believe that the Earth . . ." The education board also nominated an *ad hoc* committee to work with textbook publishers on the changes.

The requirement is the fruit of a long campaign by fundamentalists to have special creation taught alongside

Darwin's theory of evolution in schools in California (see *Nature*, 239, 483; 1972). They failed, however, to persuade the education board to take a more positive step and require that special creation should get equal time with Darwin in biology textbooks.

The board took its decision last week after 19 Nobel laureates in California had advised against it. A letter drafted by Arthur Kornberg suggested that conditional statements are justified only when there are conflicting theories put forward to explain a body of facts, and none can be eliminated by existing scientific evidence. "No alternative to the evolutionary theory gives an equally satisfactory explanation of the biological facts", the letter said.

Because California schools account for about 10 per cent of all textbooks published in the United States, the board's decision will extend beyond the borders of California—few publishing companies will publish books for California children alone.

these goals are beyond the reach of public scrutiny. . . . When the basic decisions that set the priorities for science are in the hands of powerful institutions, to rest on a claim of moral neutrality is to surrender our moral autonomy to these institutions".

But what seems to bother many members of the society is, first, how can the society, or for that matter anybody else, determine what is eventually going to benefit man; and second, how can the APS pinpoint and reject those areas of science which are judged to be harmful? To be sure, much of the specific criticism has been directed at the part of the amendment which March now wants to delete, but a number of letters printed in the same issue of *Physics Today* were openly hostile to any amendment, even the watered down version which March now hopes to propose.

March, however, says that he is not asking for a self-righteous committee to sit in judgment over members of the society, but simply for moral questions to be given a full public airing. That, he says, "would help members to face the moral and social implications of their work, matters it is often more comfortable to ignore.

If all that March and his colleagues want is a full discussion of issues relating to social responsibility, then the executive committee of the society believes that it has already provided a platform for airing such issues. Last year, on its own initiative, the executive committee set up a forum on physics and society as a formal part of the APS, through which all sorts of social questions could be discussed. But the controversy which surrounded its debut at the spring meeting this year suggests that the executive committee is already regretting its decision to establish the forum, and attempting to clip its wings.

A series of discussions of the role of physics and physicists in the Vietnam War was arranged for the forum's debut. But not surprisingly all the papers turned out to be highly political criticisms of the war, and Dr Havens, who edits the *Bulletin* of the APS, decided not to publish their abstracts alongside abstracts of all the other papers delivered at the APS spring meeting. His reason, he said, was that the papers dealt with physicists and not with physics, and therefore fell outside the scope of the society's constitution. They did, however, fit in with the by-laws of the forum on physics and society, a contradiction which suggests that the forum itself is in an ambiguous position with regard to the society's constitution. March therefore argues that his amendment will "add further legitimacy to the efforts of the forum, by acknowledging that its activities are an integral part of the

goals of the American Physical Society".

Underlying some of the pressure for change in the APS is the feeling that its original aim—to promote interchange between physicists—is being fulfilled by other channels of communication. Few scientists save up their cherished results for presentation at a meeting of the society, for example. (That being the case, it is not surprising that the vast majority of the APS's 28,000 members are unaware of, or unconcerned with, the debate about the society's constitution, since they are primarily concerned with getting the APS publications.) One of March's chief points, however, is that the APS is still the main professional society for physicists, and he suggests that "most other professions with as much social impact as physics have long since publicly acknowledged their moral responsibility. Some have not. The Cosa Nostra, for example, piously claims ethical neutrality. I would prefer to see my profession in better company."

TECHNOLOGY

Computer Control

by our Washington Correspondent

THE widespread belief that the use of computers to store information about individuals in the United States is rapidly eroding civil liberties and prematurely ushering in the nightmare world of Orwell's *1984* is, according to a report published last week*, highly misleading. The thesis of the report, which was nearly four years in the making, is that potential abuses of privacy and civil liberties were inherent in record-keeping by government, corporations and law enforcement agencies before the advent of computers, and have been carried over into the computer age. Computerization *per se* has not greatly increased the potential for abuse, nor does it offer a means for safeguarding personal liberties—that is up to the courts and legislators.

Those conclusions do not, however, lead the authors of the study to recommend that no fresh safeguards are needed to protect privacy and civil liberties—far from it. The authors of the report, Alan F. Westin, professor of public law at Columbia University, and Michael A. Baker, instructor of sociology, Brooklyn College, City of New York, recommend that individuals should have more right of access to the information contained on files of all kinds, and that the collection of unnecessary personal data should be curbed. They see the onus for these reforms falling chiefly on the shoulders of legislators.

Given the widespread use of files and

personal data in all facets of American life, the rapid growth of the civil liberties movement in the 1950s and 1960s and the disenchantment among young people with authority and corporate power in the late 60s and 70s, it is not surprising that there is widespread distrust of computerized databanks in the United States. A national survey of college students conducted in 1971, for example, found that 83% of the respondents agreed with the statement that "people's privacy is being destroyed", and in the population as a whole, 62% of respondents in a survey last year said that they are "very" or "fairly" concerned about the information that some organizations are keeping about people in their files.

What steps can usefully be taken to safeguard civil liberties in the use of computerized databanks? The first thing to be said is, according to the authors, that "no single law, constitutional amendment, or court decision can cope with the tremendous diversity of issues and settings, and the uneven readiness for corrective action that make up the current databank problem". They therefore reject the much touted suggestion that supervisory agencies should be set up in each layer of American government to oversee the creation of all computerization of databanks to ensure that civil liberties will be safeguarded. There is no guarantee, they say, that such an institution would be any more sensitive to issues of privacy than existing government agencies or legislative committees.

Westin and Baker believe that a more constructive approach should give the citizen more information about the type of data that is held on government files, and that he should have access to most of the files to make sure that they are correct. They believe that all those files used for administrative purposes should be open for inspection and only those used for intelligence should be closed.

As for data sharing brought about by computerization, Westin and Baker suggest that only some credit reporting firms are making extensive use of the potential for interconnecting databanks. They note that extensive information sharing could have important implications for civil liberties, however, and emphasize that although large interconnecting databanks have not yet emerged, "we are not saying that central databanks within single organizations or as jurisdictionwide systems are technologically impossible, or that they will never be built". Overall, however, they see problems of privacy connected with databanks as sociological in origin rather than technological.

**Databanks in a Free Society*, by Alan F. Westin and Michael A. Baker. Quadrangle Books, \$12.50. Conducted under the auspices of the National Academy of Sciences.

NEWS AND VIEWS

Neurosecretion in the Test Tube

BIOCHEMISTS delight in converting the complex cellular structure of animal tissue into pipettable liquid soups by means of homogenizers, blenders and other instruments of controlled destruction. The application of such procedures to the extraordinarily heterogeneous and complex architecture of brain tissue has been known to make neuro-anatomists wince, and others with some understanding of the nature of the insult thus inflicted may understandably question the wisdom of such destructive attacks.

It has been apparent for the past ten years, however, that some very fortunate and useful things happen to brain tissue during homogenization. Whittaker and his colleagues and De Robertis and his group opened up an important new approach to neurochemical studies in the early 1960s by their discovery of synaptosome particles in brain homogenates. Large numbers of such particles, representing membrane-bound structures, derived from the pinching-off and resealing of nerve endings, form when brain tissue is homogenized in an isotonic sucrose medium. Synaptosomes represent an enriched source of neurotransmitters and their related enzymes and storage mechanisms, and they can be separated from other sub-cellular particles present in the homogenates by density gradient centrifugation procedures.

During the past few years it has, furthermore, been found that isolated synaptosomes are capable of maintaining a surprising variety of metabolic and neurotransmitter-related functions *in vitro*. Thus, Bradford (*Brain Res.*, **19**, 239; 1970; and in earlier studies) showed that synaptosomes are capable of sustaining high rates of respiration when incubated in glucose-containing buffered artificial salt media, and that a selective release of neurotransmitter amines and amino-acids could be evoked from such particles by electrical stimuli, or by exposure to high external potassium concentrations to cause depolarization of their membranes. Snyder and his colleagues (Logan and Snyder, *Nature*, **234**, 297; 1971) have shown that synaptosome particles offer a useful *in vitro* system for studies of the various specific high affinity uptake systems for amines and amino-acid transmitters that exist in the different categories of neurone in the brain.

Edwardson, Bennett and Bradford describe, on page 554 of this issue of *Nature*, an important new application of synaptosomes as a model for studies of neurosecretion *in vitro*. It has previously been established that homogenates of brain tissue dissected from the base of the hypothalamus contain a special category of synaptosome representing the pinched-off terminals of the neurosecretory neurones present in this brain structure. Such synaptosomes contain many, and probably all, of the various different hypothalamic "releasing factor" peptides, which play a key part in the nervous control of pituitary function and the synaptosome preparations also contain vasopressin and oxytocin. Edwardson *et al.* show that synaptosome preparations of this type can be used as model systems for studying the release of these peptides in the test tube.

A synaptosome fraction was prepared from sheep hypothalamic tissue, and the synaptosomes were incubated in

a balanced salt medium in vessels especially fitted with electrodes so that the contents could be subjected to electrical field stimulation. Alternatively the synaptosomes were stimulated by depolarizing concentrations (55 mM) of potassium. Both types of stimulation caused a release of three peptides—corticotropin releasing factor (CRF), vasopressin and prolactin inhibitory factor (PIF)—into the incubating medium. Stimulation caused a five to ten-fold increase in the rate of release of the first two substances. The released peptides were estimated by bioassay, and also more directly by their effects on ACTH or prolactin secretion from anterior pituitary tissue incubated *in vitro*.

In parallel experiments it was also found that synaptosomes prepared from the sheep hypothalamic tissue selectively release the putative transmitter amino-acids glutamate, aspartate and gamma-aminobutyrate on stimulation, as previously found by Bradford (1970). Electrical stimulation resulted in the release of more than 50 per cent of the total synaptosome content of these three amino-acids into the incubating medium, whereas less than 10 per cent of the content of the non-transmitter amino-acids glutamine, serine, glycine and alanine were released.

These experiments should give cause for excitement to neuroendocrinologists and to neurochemists. It is clear that the synaptosome system offers many new possibilities for studying the complex factors which control the storage and release of hypothalamic neurosecretory peptides; processes that are difficult or impossible to study *in vivo*. Edwardson *et al.* hint that it may also be possible to study the biosynthesis of the releasing factors in this test tube system. It seems that the audacious assaults inflicted on central nervous tissues by the biochemist can sometimes and release of hypothalamic neurosecretory peptides, pay handsome dividends.—From our Neuropharmacology Correspondent.

Oceanic Microearthquakes

DURING the past five years or so, the development of efficient portable seismograph stations and dependable, low-cost telemetry systems for transmitting seismic data continuously by radio or telephone has led to a significant increase in the information that may be derived from the study of small earthquakes. In geological studies, one of the advantages of using microearthquakes (often taken to mean shocks with m_b less than about 3) as opposed to earthquakes of higher magnitude is, of course, that there are a lot more of them. There are thus statistical advantages to be gained once it becomes possible to detect them efficiently and to determine their basic characteristics.

The area where microearthquakes have been pursued most vigorously is probably the western United States. In California, for example, Eaton *et al.* (*Bull. Seismol. Soc. Amer.*, **60**, 1151; 1970; and *Tectonophysics*, **9**, 259;

1970) have been able to demonstrate the intimate relationship between microearthquakes and the San Andreas fault to show that microearthquakes can be used to map active faults and to determine the depth to which stick-slip motion extends. Quite apart from their intrinsic academic interest, these and similar studies are of considerable importance in the search for viable prediction techniques along the San Andreas fault and its associated faults. Members of the US Geological Survey's National Center for Earthquake Research have discovered, for example, that microearthquakes play a significant part in releasing tectonic strain as it builds up. In other words, the real danger zones are those where microearthquakes are now known to be rare and where an unmitigated build-up of strain can be expected to culminate in one or more extremely large events.

The San Andreas fault zone may be fairly regarded as an atypical part of the world rift system; and, in a rather different sense, so may Iceland, where Ward *et al.* (*J. Geophys. Res.*, **74**, 665; 1969) deployed portable seismographs at seventy-eight sites to monitor microearthquakes during the summer of 1967. Iceland, of course, has never been studied as intensively as the San Andreas region, so at the time that Ward and his colleagues began their work it was not even possible to plot the course of the Mid-Atlantic Ridge through the country with any degree of certainty. Ward *et al.* were therefore able to apply the statistical advantages of microearthquake investigation to a relatively unknown situation and, in so doing, were able to propose the existence of two transform faults within Iceland and plot their positions with some conviction. Subsequently, Molnar and Aggarwal (*Bull. Seismol. Soc. Amer.*, **61**, 195; 1971) successfully used similar instruments and techniques in the Kenyan section of the East African rift.

But the three examples quoted so far have been based on land areas where access is relatively free. Any attempt to extend such studies to the ocean bottom, where, after all, the world rift system is at its most "typical", clearly poses additional practical problems. The Mid-Atlantic Ridge far from Iceland is a good case in point. As Francis and

Porter point out on page 547 of this issue of *Nature*, accurate correlation of seismicity and physiography has hitherto not been possible because of the crudity of epicentral location far from continents; depth determinations have been limited, on the whole, to qualitative descriptions such as "shallow". The need is clearly for seismographs on the ocean floor if any further progress is to be made in the detailed seismological study of ridge axes.

Instruments for ocean bottom seismology have been under development for some time, although as recently as 1970 one author pointed out that such instrumentation is only in its early stages. Three basic approaches have been tried. In the first, a sealed seismograph is lowered to the ocean floor from a ship and the seismic signals are telemetered back to the ship by cable. The disadvantage of such a physical link is the obvious one—that motions of the ship and the connecting cable tend to be transmitted to the instrument. The technique has, however, been used with some success on the floors of the Black Sea and the Baltic by Soviet seismologists. The solution to this problem is to replace the cable by an acoustic link, and this, too, has been made to work successfully. A third

method involves the use of a self-contained detecting and recording package which is dropped to the ocean floor and subsequently recovered for analysis at an appropriate time.

In Britain, an ocean bottom seismograph developed jointly in recent years by the Institute of Geological Sciences and the UK Atomic Energy Authority adopts the third of these approaches, although a subsidiary instrument-to-ship acoustic link is used for position measurement. Francis and Porter describe microearthquake data obtained from the first deployment of two of these instruments—one of which was dropped some 30 km to the east of the median valley of the Mid-Atlantic Ridge and one of which was placed in the median valley itself. The results are, of course, preliminary, but two things are already clear. The first is that because of the characteristics of the ridge zone, the best results will only be obtained from arrays of seismographs with instrument spacings of less than 10 km. The second is simply that the deployment of such arrays, as on land, will pay handsome dividends in terms of data from what is one of the key zones of the new global tectonics.—From our Geomagnetism Correspondent.

Temperature Sensitive Mutant Mammalian Cells

THE isolation and characterization of conditional lethal mutants has been a cornerstone of the analysis of metabolic pathways in bacteria and several groups are currently attempting to isolate temperature sensitive mutants of mammalian cells growing in culture and then to use them to analyse such processes as DNA replication, transcription, mitosis and so on.

It has already become apparent that many cultivated cells with mutated phenotypes have high reversion rates which not only hinder biochemical analyses but also raise questions as to the nature of the genetic changes which lead to the changed phenotype. Chromosomal and therefore gene dosage effects may, for example, be important. But as Naha reports in *Nature New Biology* next Wednesday (January 3) it is possible to select clones of African green monkey kidney BSC 1 cells that are temperature sensitive for cell proliferation and have reversion frequencies of less than 10^{-5} .

Naha has, apparently, isolated eight such mutant clones which can be classified into three groups by virtue of their phenotypes at the non-permissive tem-

perature (39.5° C). The first group of mutants is defective in thymidine metabolism; the second group is defective in uridine metabolism and the third group is defective in both thymidine and uridine metabolism. These lesions reduce by more than ten-fold the plating efficiencies of the cells at 33° C after they have been held for 12 h in 39.5° C and from analyses of cell generation times Naha concludes that it is likely that mutants of the second and third groups are blocked early in the G1 phase and mutants of the first group are blocked in the S phase of the cell cycle.

Analysis of the fate of ^3H -thymidine incorporated during a 30 minute pulse at 39.5° C indicates that TTP accumulates in these cells which are blocked in DNA synthesis and the decrease in viability with time at the non-permissive temperature suggests that the defects they carry become irreversible. Precisely which steps in the pathway to DNA synthesis are defective remains to be seen; as Naha comments, it also will be particularly interesting to see if infection by SV40 at 39.5° C overcomes the block to DNA synthesis in these cells.

PREHISTORY

Ancient Astronomy at the Royal Society

from a Correspondent

THE large lecture theatre at the Royal Society was full throughout the two-day meeting on "The Place of Astronomy in the Ancient World", which was held on December 7 and 8 and organized jointly by the Royal Society and the British Academy. The aim of the meeting was to integrate contributions from the realms of astronomy, ancient history, archaeology and anthropology. Most of the audience seemed to agree that the experiment succeeded: few who attended the meeting can have departed without experiencing a rapid widening of their horizons.

The meeting began with an admirable introduction to the basic astronomical concepts by Dr R. R. Newton (Johns Hopkins University). After that came surveys of the "written evidence". Professor A. Aaboe (Yale University) reviewed scientific astronomy in antiquity, with particular emphasis on Babylonian mathematical astronomy, including the methods of predicting the motion of the Moon and Mars. Professor R. A. Parker (Brown University) described ancient Egyptian astronomy with its emphasis on the heliacal risings of stars, and its achievement in defining the calendar still used today. (Indeed, we still follow the Babylonians in dividing hours and minutes into sixty parts.) Professor A. Sachs (Brown University) discussed Babylonian observational astronomy, particularly as recorded in the detailed astronomical diaries between 600 BC and 50 BC.

After this settled start in the Middle East, the audience was whisked to and fro across the world, first to Mexico, where Dr J. E. S. Thompson, out of his unrivalled knowledge of the Maya, explained their activities in astronomy. Although they were much concerned with eclipses, the Maya really did best with their observations of Venus, whose synodic period they calculated to an accuracy of 1 part in 2 million. Returning to Europe, Dr R. R. Newton gave an arresting account of the possible errors in interpreting ancient and mediaeval descriptions of solar eclipses, which he has used in his work on measuring the deceleration in the Earth's rotation. The final contribution on literate astronomy was a masterly survey by Dr J. Needham (University of Cambridge) of astronomy in ancient China, which was from early times couched in polar and equatorial, rather than planetary and ecliptic, terms.

The first contribution on the unwritten evidence, on Polynesian and Micronesian astronomy, came from Dr D. Lewis (Australian National Univer-

sity), the only author unable to be present (because he is now on a solo circumnavigation of Antarctica). For the South Sea islanders astronomy is equated with navigation, and Dr Lewis has obtained astronomical sailing instructions, hitherto handed down in secrecy, which prove to be remarkably accurate for journeys between islands. From the South Seas to neolithic Europe was the next step, as Professor R. J. C. Atkinson (University College, Cardiff) presented a fine survey of neolithic science and technology in north-west Europe about 4000 BC and 1800 BC. He emphasized the great skill in engineering required to transport and elevate stone blocks weighing 50 tons or more, and to mine the chalk for flints.

The next speaker was Professor A. Thom, who summarized his remarkable work during the past twenty years on how the late neolithic peoples of north-west Europe built astronomical observatories in stone to record the extreme setting points of Sun and Moon, measured the obliquity of the ecliptic in ancient times and discovered small perturbations in the lunar inclination. Professor G. S. Hawkins (Smithsonian Astrophysical Observatory) then described his work on the analysis of photogrammetric air surveys of Stonehenge, the temple of Amon-Ra at Karnak, and the desert lines near Nasca, Peru. The desert lines are extraordinarily straight and accurate, but his detailed analysis has revealed no significant links with declinations relevant to astronomy: for a country where Sun-worship flourished his conclusion

is disappointing, yet also most valuable as an answer to those who dismiss the astronomical significance of alignments by saying that significance can be found in any set of lines.

Professor H. H. Lamb (University of East Anglia) presented a wide ranging review of climate, vegetation and forest limits in early civilized times. His maps of the average atmospheric pressure at sea-level around 2000 BC showed that in north-west Europe those "halcyon days" were less windy, and probably drier and sunnier, than at present. Dr E. W. MacKie (University of Glasgow) reported the results of an excavation at a small platform on a remote Scottish mountainside, which, suggested Professor Thom, must have been used initially in setting up an astronomical sight-line. Dr MacKie has unearthed evidence that the platform is man-made. In the final contribution the audience enjoyed a fascinating exposition of how to hunt quanta, by Professor D. G. Kendall (University of Cambridge). He not only hunted a quantum of length, but found it after a detailed statistical study of 169 stone circles; he thus confirmed (with the usual caveats about significance in a finite sample) the reality of Professor Thom's favourite concept of the "megalithic yard" of 1.66 metres.

Although the meeting was chiefly successful in building a bridge between scientists and historians—by making them meet each other and experience the other's modes of thought—the meeting was memorable in other ways too. It marked something of a triumph for Professor Thom. His thesis that many ancient standing stones in north-west Europe represent accurate astronomical sight-lines, either solar or lunar, has in the past met strident opposition. But at the lengthy discussion sessions during

Variations in Repeated Genes

THERE has been some argument about the proposition that the sequences of the multiple repeated genes of eukaryotes are really identical. Working with *Xenopus* 5S RNA, for which there are several thousand clustered genes, Ford and Southern report in next Wednesday's *Nature New Biology* (January 3) that there is in fact sequence heterogeneity.

A comparison of oligonucleotide maps of 5S RNA digests from ovary and kidney cells reveals considerable differences; six base changes can be recognized with certainty, and it cannot be excluded that others are present that have not yet been detected. Of the six substitutions, four occur in a small part of the sequence—between positions 47 and 56. Furthermore, it can be deduced from the nucleotide maps of the ovary 5S RNA that its sequence is not homo-

geneous, some components being present in submolar amounts; these mostly represent spots characteristic of this kidney 5S RNA. Contamination is excluded as an explanation of these components, because the RNA was extracted from a high-molecular weight particle, peculiar to the ovary.

The yields of the nucleotides indicate that at least four sequences exist in appreciable concentration in the ovary 5S RNA, and further minor components may also be present. The same patterns are generated from the ovaries of different *Xenopus* individuals, and do not therefore represent alleles of one locus.

Ford and Southern have considered possible biological interpretations of these findings; they favour the view that the different sequences correspond to different functional requirements.

this meeting his opponents were distinctly subdued, especially after his allied concept of the megalithic yard had received Professor Kendall's blessing.

Some at least of the participants also felt that the meeting took on a life of its own, as an unintended (and therefore all the more sincere) tribute to those nameless but ingenious proto-scientists of antiquity: the Babylonians and Egyptians who gave us our timing systems; the Polynesian navigators; the neolithic European engineers and miners; the Maya, who timed Venus so exactly; and, perhaps most of all, the ancient Britons who found how to measure the lunar inclination. Although presumably illiterate, they seem to have developed methods of astronomical measurement fundamentally much more accurate than any devised by an ancient literate society.

PROTEIN SYNTHESIS

End of Message

from our Molecular Biology Correspondent

IN a fast moving field, like control of eukaryotic protein synthesis, there is a tendency to make a little, in the way of results, go a long way. New discoveries do not in consequence hit the literature with a solid and reassuring thud that draws the reader's attention, but come instead in the form of a continuous spatter of grapeshot. This makes all efforts to keep abreast of progress doubly irksome, yet from time to time some small advance may actually be discernible from the outside. An interesting aspect, about which there has been a considerable effusion of articles in the past year or two, is the run of polyadenylic acid, which seems to occur at the 3'-end of nearly all eukaryotic messengers, is not translated, and has no obvious function. Now Kwan and Brawerman (*Proc. US Nat. Acad. Sci.*, **69**, 3247; 1972) have found evidence that it is the anchoring point of some at least of the protein that accompanies the messenger into the cytoplasm and on to the polysomes, and stays with it when it is dissociated from the polysomes by treatment with EDTA for example.

The poly A segment is easily enough prepared from the isolated (protein-free) messenger by treatment with pancreatic ribonuclease and sediments at about 4S. Working with the ascites cell system, Kwan and Brawerman find that the particle remaining, after an extensive nuclease digestion of the polysomes, sediments at 12-15S, and when deproteinized with detergent yields the 4S poly A fragment. Its complement of proteins has not evidently been picked up from the debris of polysomes and degraded messenger, for the poly A

piece derived from ^{14}C -labelled messenger, digested with nuclease in the presence of tritium-labelled polysomes did not generate a 15S particle. (Some interaction with the protein mixture does nevertheless occur, for a fraction sedimenting somewhat faster than 4S seems to be generated.) The inference is that the poly A end of the messenger does indeed carry proteins. These are sufficient to afford the poly A at least partial protection against the A-specific T_2 -ribonuclease. The poly A, or a part of it at least, is yet sufficiently unimpeded to form a complex with added polyuridylic acid.

The functional relevance of these results, of course, remains unexplained, for nothing is in fact known about the role of the messenger-bound proteins, neither does the fact of their association with the poly A end throw much light on any role that this may have in the process of messenger migration. Moreover, Kwan and Brawerman have not ascertained whether the protein fraction in the poly A particle accounts for all the recognizable proteins that are carried by the messenger. The high sedimentation rate (30-150S compared with 10-30S for the messenger RNA alone) of the messenger-protein complex, and its high buoyant density, indicate, as Kwan and Brawerman point out, that it may not.

When cells in culture are treated with 3'-deoxyadenosine, the turnover of messenger largely ceases, and it now seems, from some results of Adesnik *et al.* (*J. Mol. Biol.*, **71**, 21; 1972), that this may arise from a disturbance in the mechanism of grafting the poly A onto the newly transcribed messenger RNA. The deoxyadenosine does not bring

about the complete disappearance of messenger: the concentration of a nucleotide label in the product of EDTA-dissociation of the total polysomes indicates that the messenger content of the cytoplasm is 10-20 per cent of the normal level. Of this some 70 per cent binds to captive poly U, covalently attached to a column matrix, and is little different from the fraction that binds in normal cells. It thus seems that the poly A is present in the existing messenger. After nuclease digestion, however, the total proportion of nucleotide retained on the poly U column was a good deal less than that from normal messenger. Analysis by polyacrylamide gel electrophoresis of this nuclease-resistant residuum showed that the messenger in the polysomes of the poisoned cells had a smaller and more polydisperse complement of poly A than that of normal cells.

The abnormal messenger is, all the same, incorporated into polysomes to the normal extent. A chase experiment with actinomycin, which stops all RNA synthesis in the nucleus, indicated that the 3'-deoxyadenosine operates by preventing the migration of messenger into the cytoplasm. It is known to inhibit the incorporation of A residues into RNA, so that one may suppose that it strangles the supply of nucleotides needed for the addition of poly A to the completed messenger, and further that a critical length of poly A is indispensable for the transport process. It would be of some interest to establish whether this might not also be the length required for the retention of one or more of the proteins that, according to the results of Kwan and Brawerman, travel on the poly A.

What Generates the Cohesive Ends of Lambda?

DURING various stages of the life cycle of bacteriophage lambda the circular duplex DNA genome of the phage is converted into a linear duplex molecule which, because of its cohesive ends, can return to its circular duplex form. Several pieces of evidence indicate that these changes are neatly achieved by introducing single chain scissions, staggered by twelve bases, in the complementary strands of the circular duplex DNA. But what endonuclease, or endonuclease complex, presumably specified by the lambda genome, is responsible for this specific nucleolytic attack? This question has yet to be fully answered, but experiments reported in *Nature New Biology* next Wednesday (January 3) by Wang and Kaiser indicate that a product of the lambda gene A is required.

Using a biological assay system for linear lambda DNA molecules, Kaiser and Wang have shown that extracts of

Escherichia coli infected with wild type lambda contain an activity which *in vitro* will convert circular monomeric and dimeric lambda DNAs into linear molecules with cohesive ends. This reaction depends on a supply of ATP, which is a characteristic requirement of many endonucleases. Furthermore, it also depends on an activity specified by gene A—extracts of cells infected with lambda carrying a mutated gene A or a gene A deletion do not convert circular DNA into linear DNA.

The A gene product required for this reaction is almost certainly a protein because it is temperature sensitive and because amber mutants of the A gene have been isolated. Wang and Kaiser suggest, from these and other data, that the A gene product is a specific endonuclease responsible for generating cohesive ends, but proof that this is the case will depend on the isolation and purification of the gene A protein.

AUXINS

Hormone Action

from our Plant Biochemistry Correspondent

THE molecular mechanism whereby auxins and other hormones control the growth and development of plant cells is currently receiving a great deal of attention. Early suggestions that hormones may control the rates of transcription and/or translation were apparently confounded by the many recent findings of very rapid effects of auxins. They were therefore generally discarded in favour of rather vague hypotheses involving effects on membrane properties. Rapid effects on membranes and slower effects on gene expression, however, are not necessarily incompatible as is shown by a report by Hardin, Cherry, Morré and Lembi (*Proc. US Nat. Acad. Sci.*, **69**, 3146; 1972).

Hardin *et al.* present evidence that auxin treatment of isolated plasma membrane fractions of soybean hypocotyls leads to the release from the membranes of a transcriptional factor which significantly stimulates the activity of soybean RNA polymerase. Although the two auxins indoleacetic acid (IAA) and 2,4-dichlorophenoxyacetic acid (2,4-D) released the transcriptional factor, the non-auxin structural analogue 3,5-dichlorophenoxyacetic acid (3,5-D) did not. Plasma membrane fractions which had been pretreated with 3,5-D, on the other hand, subsequently released the transcriptional factor when treated with 2,4-D, demonstrating the specificity of the response towards authentic auxins.

Seen in the light of other recent and related findings, these observations are clearly important. The specific reversible binding of auxins to plasma membrane fractions from maize coleoptiles has been demonstrated (within the limits of available techniques) by the recent work of Hertel, Thomson and Russo (*Planta*, **107**, 325; 1972) who calculated an apparent K_M for binding of between 10^{-6} M and 10^{-5} M for IAA and for a further auxin α -naphthaleneacetic acid (NAA). The concentration of specific binding sites was about 10^{-7} to 10^{-6} M per tissue volume, corresponding to every 50th to 200th subunit of the plasma membrane.

The methods of sub-cellular fractionation of plant materials are still very crude, of course, and as Hertel *et al.* point out, further characterization of the auxin-binding components will be necessary before their identification as plasma membrane can be considered unequivocal. There are other indications, however, that auxins interact *in vitro* with the plasma membrane. VanDerWoude, Lembi and Morré earlier this year showed that 2,4-D treat-

ment of plasma membrane fractions from onion stems increased the activity of a glucan synthetase (*Biochem. Biophys. Res. Commun.*, **46**, 245; 1972). This enzyme, which has a relatively low affinity for UDP-glucose, in contrast to the glucan synthetase from dictyosomes, is considered to be a marker enzyme for the plasma membrane.

There has also been support recently for the idea that auxins interact with RNA polymerase by way of a transcription factor. Mondal, Mandal and Biswas (*Nature New Biology*, **240**, 111; 1972) describe experiments in which a protein isolated from the nucleoplasm of coconut endosperm nuclei binds to added IAA and the resulting complex stimulates DNA-dependent RNA synthesis using coconut endosperm RNA polymerase and DNA. In this case, not only has an increased synthesis of RNA been shown, but there is some evidence using polyacrylamide gel electrophoresis that the types of RNA synthesized may also be changed. Auxin acceptor pro-

teins that can alter the rate of *in vitro* RNA synthesis have been reported before (for example, Matthysse and Phillips, *Proc. US Nat. Acad. Sci.*, **63**, 897; 1969), but they were only effective with chromatin preparations and not with DNA. Venis has also described (*Biochem. J.*, **127**, 29p; 1972) the isolation by affinity chromatography of auxin (2,4-D) acceptor proteins from pea and maize shoots. These factors, when eluted from the 2,4-D-agarose columns, increased RNA synthesis supported by *E. coli* RNA polymerase by up to 300 per cent.

All this evidence does not at present fit into a simple hypothesis. The work of Hardin *et al.* implies that auxin binds to the plasmalemma and causes the release of a substance which itself stimulates RNA synthesis, whereas most of the other work mentioned suggests that auxins bind directly to non-particulate receptor proteins which are thereby activated to stimulate RNA synthesis. The very fact that so many auxin effects

Failure of Self-tolerance *in vitro*

IMMUNOLOGICAL tolerance was outlined as a phenomenon by Burnet and Fenner in 1949. Their basic postulate was that cells capable of reacting against self-antigens are eliminated during the development of immunologically competent lymphocytes. If this were true they predicted that introduction of foreign antigens at the appropriate stage of development would lead to a state of specific unresponsiveness as a result of the elimination of those cells capable of reacting against the foreign antigen. The subsequent demonstration by Medawar and by Hasek that the prediction was in outline correct laid the foundation for many studies on immunological tolerance but, in spite of these efforts, the underlying mechanism remained elusive.

More recently it has become fashionable to think of immunological tolerance as not a passive condition, such as is required by the clonal elimination of Burnet, but more as a situation in which the normal manifestations of specific immunity are blocked by some serum factor. On this basis specific failure to reject a skin homograft by a mouse that has been rendered tolerant by an injection of the appropriate foreign spleen cells soon after birth is not caused by the lack of reactive cells but by the existence of a serum factor which prevents the reactive cells rejecting the skin graft. The serum factor has been thought of as an antibody, an antigen-antibody complex and as antigen. The report by Wekerle *et al.* in next Wednesday's *Nature New Biology* (January 3) impinges solidly on these matters.

Wekerle *et al.* show that inbred Lewis rat lymph node cells, when incubated *in vitro* with Lewis rat fibroblasts, develop the capacity to kill the syngeneic fibroblasts as adjudged by the release of ^{51}Cr from appropriate target cells. Wekerle *et al.* go on to show that if they separate their lymph node cells into adherent and non-adherent species soon after their initial explanation onto the fibroblast monolayer target then the adherent cells have a considerably greater capacity to lyse the target cells than have the non-adherent. This result is interpreted to indicate that there are in a normal lymph node cell population some cells with receptors for self-antigens.

Wekerle *et al.* in their final experiment found that prior incubation of their lymph node cells in autologous serum before plating onto the target much reduced the development of cytotoxicity against the fibroblasts. Pretreatment of the target cells with autologous serum was ineffective. Wekerle *et al.* conclude that *in vivo* autoimmune reactions such as they have demonstrated *in vitro* are blocked by a serum factor which is possibly soluble antigen.

These experiments tend to coincide with the view of immunological tolerance alluded to earlier. There is, however, one possible objection. How can the authors be sure that fibroblasts *in vitro* do not express antigens different from those they manifest *in vivo*? In spite of this minor reservation it is clear that the initial formulations of Burnet are being more and more strongly questioned.

in vitro can be counted, however, is surely a favourable omen. The essential similarities with certain aspects of hormone action in animals also cannot be ignored, leading one to hope that a solution to the problem of the molecular nature of auxin action is not very far off.

DNA TUMOUR VIRUSES

Replication *in vitro*

from our Cell Biology Correspondent

It scarcely needs saying that the biochemistry of DNA replication in mammalian cells has yet to be elucidated, and although several groups have shown that nuclei isolated from one sort of animal cell or another will support limited amounts of DNA synthesis such cell free systems and their products have not been thoroughly characterized. Not the least of the problems faced by those working with isolated cell nuclei is the characterization of the DNA that the nuclei make. Mammalian DNA is so complex and the amount of DNA per nucleus is so great that characterization of any DNA made *in vitro* is at present, as Winnacker *et al.* (*J. Mol. Biol.*, **72**, 523; 1972) comment, "an essentially hopeless task". It was to avoid attempting the hopeless that Winnacker and his colleagues decided to work with nuclei isolated from mouse 3T6 cells infected with polyoma virus. Polyoma virus DNA molecules, each weighing 3.5×10^6 daltons, can at least be isolated and studied in some detail.

Last year Winnacker *et al.* (*Biochem. Biophys. Res. Comm.*, **44**, 952) reported that nuclei from such infected cells do incorporate deoxynucleotides into the replicative intermediate of polyoma virus DNA; now they have analysed this reaction more thoroughly. By centrifugation through neutral and alkaline gradients, by chromatography and by nucleic acid hybridization they have shown that a small amount of label is incorporated into covalently closed, superhelical duplex polyoma virus DNA when the nuclei are incubated in appropriate media.

The incorporation reaction depends on the presence of all four deoxynucleoside triphosphates and is stimulated by ATP, Mg^{2+} and monovalent cations. During 5 minute incubations 3HdTTP is incorporated into short chains of polyoma virus DNA, but after 30 minute incubations much of the label is found in linear polyoma virus DNA molecules of unit length. The rate of synthesis of the viral DNA varies with temperature; at 25°, 30°, and 35° C incorporation is non-linear and at all three temperatures incorporation

reaches much the same plateau level. These data suggest that viral DNA synthesis in these isolated 3T6 cell nuclei is restricted to the completion of daughter DNA chains, the synthesis of which had been initiated *in vivo*. This is not surprising because to date all mammalian cell free systems which support DNA synthesis do not apparently support new initiation events.

In a second report, the same group (Magnusson *et al.*, *ibid.*, 539) describe experiments in which they used a density label, dBrUTP, which replaces dTTP, to analyse the DNA synthesized *in vitro*; their data indicate that the synthesis of viral DNA *in vitro* is semi-conservative. And, by first labelling cells with 3H -thymidine, then extracting the nuclei and allowing them to incorporate dBrUTP and ^{14}C -dATP and finally analysing by gradient centrifugation the distribution of the two radioactive labels and the density label, these authors have been able to conclude that the daughter chains of virtually every

partially replicated polyoma virus DNA molecule present in the nuclei are elongated *in vitro* at a rate at most only 20 per cent of that *in vivo*. Whether or not the daughter chains are synthesized discontinuously as a series of Okazaki-type pieces which are ligated remains an open question. The fact that after 5 minute incubations 3HdTTP is incorporated into short DNA chains whereas after 30 minute incubations label occurs in long chains is consistent with the idea that synthesis is discontinuous, but it can equally well be argued that the rate of addition of nucleotides decreases as the chain length increases.

This is one of the several questions that Winnacker and his colleagues may be able to solve using their cell free system, and whatever else they should find that replication of circular polyoma virus DNA is a bidirectional process. This would agree with the findings of Danna and Nathans (*Proc. US Nat. Acad. Sci.*, **69**, 3097; 1972) that repli-

Building Structures from the Void

At a time when few scientists even know that "data" are plural and are given rather than taken, scientific etymology is out of fashion. Whoever pauses to ask how eutectics acquired their name? These are intimate mixtures of two or more phases, patterned in fine regular lamellae or rods, often as well ordered as a regiment on parade. The name simply means "well built". A eutectic grows when a molten alloy of the right composition is frozen. A liquid alloy is like the Earth before its formation: without form, and void-amorphous, in fact—and so the well-built structure emerges from the initial void.

Research on eutectics is in full spate: this is partly because of the intrinsic interest of the subject, and partly because of hopes of engineering applications. The interest lies in discovering what factors determine the spacing of the eutectic structure and the crystallographic relation between the phases, and the possible applications are centred on making strong and creep-resistant alloys.

In normal conditions fibre reinforced composites using glass or carbon fibres are manufactured by putting ready made fibres into a plastic, metal or glass matrix, and it has often proved very difficult by this means to get a uniform, regular and well-aligned composite, one which is literally eutectic. So a great deal of research has gone into directional solidification of molten alloys, in which heat is abstracted strictly in one direction so that the product is a single grain with one parallel set of lamellae

or rods, grown *in situ* (instead of the maze of winding lamellae or rods found in a normal ingot). By modifying composition in a ternary alloy, growth rate and temperature gradient, a variety of highly ordered eutectic structures can be designed. The technique builds on the earlier research on the basic features of eutectic solidification and is (*pace* the Manchester report) one of the more heartening examples of technology building on science.

The latest variant of the technique is to grow aligned eutectics not from liquids but from glasses, which are simply amorphous solids. Many melts can be turned into glasses, if not by slow cooling then by rapid quenching, and this method is most likely to be successful in congealing a liquid into a glass if it has a low freezing point: just this is a special feature of eutectic compositions.

In next week's *Nature Physical Science* (January 1) Carpay and Cense of Philips Research Laboratories in Eindhoven show how quenched glassy mixtures of certain salts or oxides can be turned into aligned eutectics by heat treatment in a temperature gradient well below the eutectic temperature: the gradient is best inverted so that the eutectic grows from cold to hot. Carpay and Cense have been working with model systems, not alloys, but perhaps their intriguing method can be extended to metallic systems. The most novel feature of their eutectics is the extremely fine lamellar spacing, often less than 1 μm . The technique deserves to be followed up.

cation of the circular DNA of the related Simian Virus 40 is bidirectional. Danna and Nathans have ascertained this by analysing the distribution of ^3H -thymidine incorporated into SV40 DNA molecules replicating *in vivo*, making use of the *Haemophilus influenzae* restriction enzymes to cut the SV40 DNA at eleven specific sites to yield eleven fragments. By comparing the physical order of these fragments with the order in which they are replicated Danna and Nathans found that the fragments fall into two replication groups. Replication must therefore begin at a unique origin and proceed in two directions about the circular template, a conclusion that Slazman's group (*J. Virol.*, **10**, 484; 1972) has also arrived at recently.

THERMODYNAMICS

No Carnot Dilemma?

THE efficiency of a Carnot cycle in which the hot and cold reservoirs move at relativistic speeds is not, after all, different from the efficiency when the reservoirs are stationary. This conclusion is reached by Landsberg and Johns in a recent issue of *Journal of Physics A* (5, 1433; 1972) and resolves a strange situation that has existed since 1934, when Tolman (*Relativity, Thermodynamics and Cosmology*, Oxford University Press) proposed an efficiency of

$$\eta = 1 - \gamma_h T_c / \gamma_c T_h$$

(where h and c refer to the hot and cold reservoirs) rather than the conventional expression in which the relativistic factors are absent. Other investigators later produced a similar expression but with γ_c and γ_h interchanged. Clearly an observer in a frame of reference in which one reservoir is travelling faster than the other can "beat the Carnot efficiency" in both cases.

Landsberg and Johns have reanalysed the situation, and they pay particular attention to how much of the work done by the working fluid in one cycle is actually utilizable and should therefore be included in calculations of the efficiency. They find that one of the terms in the expression for the work done has to be replaced by another which takes account of the "purely mechanical work effectively done on the reservoirs". The efficiency they calculate then reduces to the familiar form and they conclude that motion of reservoirs and/or observer leaves the thermodynamic efficiency unchanged. Landsberg and Johns also say that the correction can be estimated by imagining a process of acceleration and one of deceleration to occur before and after the Carnot cycle respectively.

Rate of Occurrence of Supernovae

THE apparently high rate at which supernovae have been occurring recently in the galaxies NGC 5253 and NGC 5236 has encouraged Wamsteker *et al.* to take a new look at the theoretical and observational basis for the accepted supernova rate. These two galaxies are a pair which are almost certainly physically related; four supernovae have been seen in the Sc spiral NGC 5236 in the past 77 yr, and in the same period two such events have occurred in the Ir II irregular NGC 5253. This is a high frequency of supernovae compared with the average for all galaxies; the system is also interesting because the two supernovae in NGC 5253 were brighter than average, whereas the four events in NGC 5236 were fainter than average.

Although Wamsteker and his colleagues point to the Crab Nebula and its pulsar as typical of the products of supernovae, there is, of course, a school of thought which holds that the Crab is atypical. But these considerations do not affect most of the work described in

next Monday's *Nature Physical Science* (January 1), which is concerned with the rate of supernovae to be expected in galaxies of different luminosity classes. Wamsteker *et al.* have made an investigation of 128 supernovae listed in van den Bergh's catalogue (*Publ. David Dunlap Obs.*, **2**, 159; 1960).

NGC 5236, for example, has an absolute brightness of -20.5 mag, which places it in the brightest category; for such galaxies, the calculated supernova rate is 0.09 yr^{-1} . NGC 5253, however, has an absolute brightness of only -17.7 mag, intermediate between the third and fourth luminosity classes; the calculated frequency in this case is about $0.05 \text{ supernovae yr}^{-1}$. In both cases, the prediction correlates well with the observations during the past 77 yr.

The occurrence of six supernovae in the pair within this period is thus reasonable for galaxies of these luminosities, but the curious difference in brightness between the supernovae in the two galaxies remains an enigma.

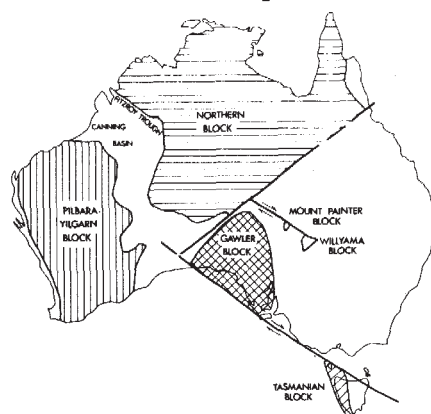
Ordovician Displacements in Australia

IN some respects, interpretations of the geology of southern Australia are not entirely satisfactory. The Precambrian-Cambrian Adelaide Orogen, for example, is sigmoidal—with an added northward spur—an odd feature which has so far received no adequate explanation. Further to the south-east, in Tasmania, Precambrian rocks outcrop on the western side of the island, but there is apparently no similar outcropping only 110 km to the north in Victoria. Moreover, whereas Cambrian volcanism is present in Tasmania in the form of predominantly acidic (and some rather more basic) volcanics, it is represented in Victoria only by greenstones. Ordovician rocks of Tasmania and Victoria are also different, although by the Silurian palaeontological and stratigraphic histories are comparable in the two states.

In next Monday's *Nature Physical Science* (January 1), Crawford and Campbell show that these and other anomalies may be removed by revoking the common assumption that all "major Precambrian welded assemblages" have acted as single units during the Phanerozoic. In other words, they maintain that the traditional concept of an Australian Platform which has been stable since the end of the Precambrian can no longer be regarded as valid.

Instead, they argue, significant horizontal displacements occurred during the Ordovician, breaking up the Precambrian blocks into smaller units. The principal Precambrian blocks of Aus-

tralia after the Ordovician displacements, together with the shear zones, are shown in the accompanying diagram. According to this interpretation there were two principal shears. The small Mount Painter and Willyama Blocks were probably broken off the Gawler Block at an earlier stage.



Finally, Crawford and Campbell suggest that the cause of the Ordovician displacements may be related to the large movement of Australia-Antarctica between the Cambrian and the Devonian that is implied by palaeomagnetic data, the point being that movement of the whole continent on such a scale is unlikely to have taken place without some internal upheaval. This is an interesting thought because it implies that similar internal adjustments should also be found on other continents which have undergone large-scale motion.

Mapping of Behaviour in *Drosophila* Mosaics

YOSHIKI HOTTA* & SEYMOUR BENZER

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By making genetic mosaics and constructing embryonic "fate maps" it is possible to locate the anatomical site of abnormalities affecting behaviour.

THE circuit components of behaviour, from sensory receptors to central nervous system to effector muscles, are constructed under direction of the genes. A mutation affecting the structure or function of any of these components may alter behaviour. Using classical genetic recombination mapping, the locus of the mutant gene within the one-dimensional chromosomal array can be determined. It is another problem to identify the "focus" of the genetic alteration, that is, the anatomical site at which the mutant gene exerts its primary effect. This might be a particular region of the central nervous system, perhaps even a single cell, or it could lie in some distant organ whose malfunction influences behaviour indirectly. The mosaic technique is a powerful method for pinpointing such a focus. Mosaics are composite individuals in which some tissues are mutant and the rest have normal genotype, making it possible to identify which part must be mutant to produce the altered behaviour.

In *Drosophila* mosaics¹⁻³, it is sometimes observed that an effector organ (for example, a leg) of mutant genotype shows normal behaviour, or vice versa. This is not too surprising, for the function may be controlled, not by the organ itself, but by an internal element such as a motor neurone in the thoracic ganglion. In some mosaic individuals, the neurone could have a different genotype from the leg cuticle, because the two structures arise from different regions of a mosaic embryo. While the cuticle genotype can be identified with genetic markers such as yellow, the genotype of the ganglion is not evident on the surface. This paper describes a method for constructing maps of internal behavioural foci with reference to external body landmarks. It is an extension to behaviour of the fate map idea conceived by Sturtevant⁴ and developed by Garcia-Bellido and Merriam⁵. Thanks to the correspondence between the positions of cells on the *Drosophila* blastula surface and the future body parts they will form, it is possible to construct a two-dimensional fate map of the blastula and to locate a mutant behavioural focus on this map. From the position of the focus, the corresponding adult tissue can be inferred. Thus, certain mutants will be shown to behave abnormally because of defects in a sense organ, others because of aberrations of the central nervous system, and others because of abnormal effector muscles.

Formation of Mosaic Flies

The method of generating *Drosophila* mosaics used in this paper depends on loss of an unstable, ring-*X* chromosome, $\text{In}(1)^w{}^c$, (here designated as X_R) during the first division of the zygote nucleus of a female embryo⁶. When this occurs, it gives rise to two clones of nuclei, one having a single *X* chromosome, the other having two. Suppose that recessive genes for visible characters such as eye colour, cuticle colour, and bristle shape are placed, by recombination, together with a recessive behavioural gene, onto the other *X* chromosome, designated X^* . In an X^*X_R embryo where the X_R chromosome carrying the normal alleles of these genes is lost, a mosaic fly is produced containing some X^*O parts in which the

behavioural gene is uncovered; these parts are identifiable by the various visible markers, at least so far as the surface of the body is concerned.

Fig. 1 illustrates typical mosaic flies, in which the XO portions (identified by the expression of male characteristics and/or recessive surface marker genes) are shown in white, while XX portions (female, normal eye colour, normal cuticle colour, normal bristles) are indicated in black. The distribution of normal and mutant areas can occur in many different ways, the dividing lines tending to follow intersegmental boundaries and the longitudinal midline. The reason for this lies in the mechanism of assembly of the adult exoskeleton, which is illustrated in exploded view in Fig. 2. Each indicated part is produced independently, during metamorphosis, from an imaginal disk in the larva⁷, which is in turn derived from a specific area of the blastoderm. For example, the right half of the main head capsule, including one eye and one antenna, develops separately from the left; the two mirror-symmetric halves are later sutured smoothly at the midline. The halves of the proboscis and of the clypeo-labrum are added, to form a complete head. In a mosaic, if the imaginal disks giving rise to two adjacent structures have different cell genotypes, the boundary on the cuticle surface follows the sutures, thus producing the characteristic patterns of Fig. 1. If the boundary in the embryo passes through the cell group for an imaginal disk, the corresponding adult part will be mosaic.

The orientation of the boundary depends on early events in development (Fig. 3). In *Drosophila*, the first nuclear division spindle is arbitrarily oriented in each egg⁹. The first nine nuclear divisions occur in a syncytium-like cluster, without cell membranes being formed. Within this cluster, little

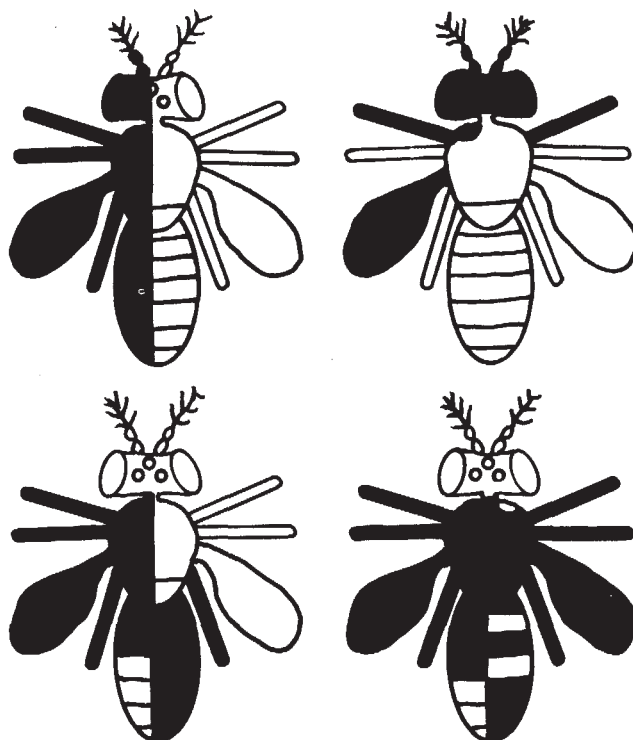


Fig. 1 Typical *Drosophila melanogaster* mosaics. Body parts derived from the XX cell line (shaded) are female. Parts derived from the XO line (unshaded) are male and also express recessive mutant characters uncovered by loss of the other *X*.

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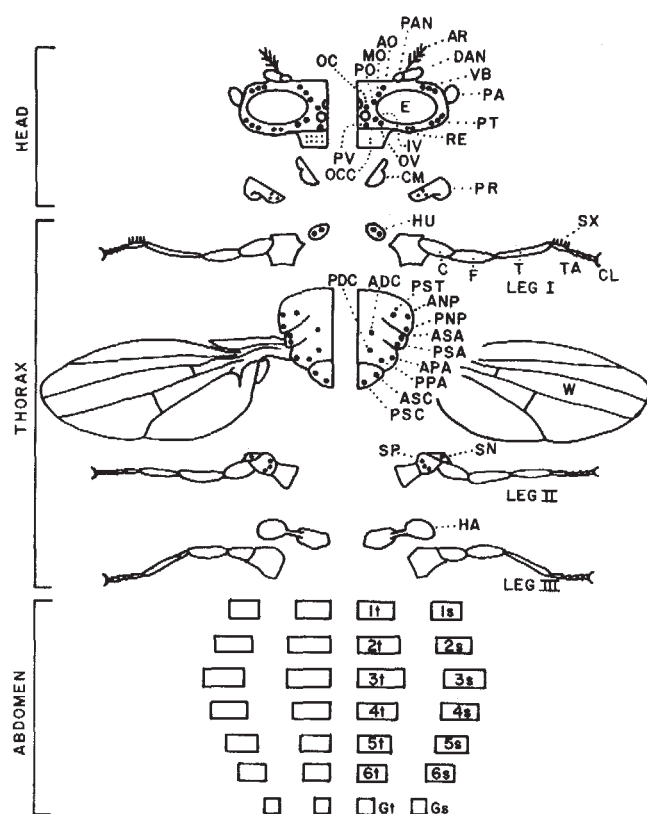


Fig. 2 Exploded view of the external body parts of an adult fly. Each part is formed independently from an imaginal disk (or similar primordium) present in the larva. During metamorphosis, the parts develop into the adult form and are sutured together to form the exoskeleton. Internal organs are not shown. Abbreviations: ADC, anterior dorsocentral bristle; AO, anterior orbital bristle; ANP, anterior notopleural bristle; APA, anterior postalar bristle; AR, arista; ASA, anterior supraalar bristle; ASC, anterior scutellar bristle; C, coxa; CL, claw; CM, clypeo-labrum; DAN, distal segment of antenna; E, eye; F, femur; Gt, genital tergite; Gs, genital sternite; HA, haltere; HU, humeral bristles; IV, inner vertical bristle; MO, medial orbital bristle; OC, ocellar bristle; OCC, occiput; OV, outer vertical bristle; PA, palp; PAN, proximal antenna (segments 1 and 2); PDC, posterior dorsocentral bristle; PNP, posterior notopleural bristle; PO, posterior orbital bristle; PPA, posterior postalar bristle; PR, proboscis; PSA, posterior supraalar bristle; PSC, posterior scutellar bristle; PST, presutural bristle; PT, postorbital bristles; PV, post-vertical bristle; RE, retroorbital bristles; SP, sternopleural bristles; SN, sternal bristle; SX, sex comb; T, tibia; TA, tarsus; VB, vibrissae; W, wing; 1t, first abdominal tergite; 1s, first abdominal sternite.

mixing apparently occurs; the relative positions of the nuclei tend to be maintained. The nuclei then migrate to the surface of the egg, where they divide three more times. Cell membranes are laid down, and a two-dimensional blastoderm, one cell thick, is formed¹⁰. Thus, if the X_R chromosome is lost at the first division, the resultant clones of X^*X_R and X^*O nuclei each populate half the blastoderm area. Assuming little mixing, the boundary is a closed figure girdling the egg surface; its layout in each mosaic depends on the orientation of the first spindle.

Once the blastoderm is formed, the site occupied by a cell largely decides its fate¹¹⁻¹³. Anterior regions produce anterior adult parts¹⁴. Cells in a defined area on the right half of the egg will give rise to the imaginal disk for the first right leg, another the right half of the proboscis, and so on, with homologous sites on the left half of the egg. The farther apart any two blastoderm sites are, the greater is the probability that the randomly oriented boundary in a mosaic blastula will pass between them. Sturtevant recognized that such probabilities could be used to construct a map of the blastoderm. This is analogous to the construction of the one-dimensional map of

the order of genes on a chromosome based on the frequencies of crossing over between the genes (an idea also due to Sturtevant), with the difference that the fate map is in two dimensions.

Map for Surface Landmarks

Consider two ipsilateral sites A and B on the blastoderm (Fig. 4), each being the primordium of a corresponding adult surface landmark. If the mosaic dividing line falls between them, they will be of opposite genotype; the probability that this will occur is greater the larger the (arc) distance between A and B. To determine that distance, many mosaic flies are examined and the following table constructed.

Surface landmark A	Surface landmark B	
	Normal	Mutant
Normal	a_{11}	a_{10}
Mutant	a_{01}	a_{00}

where a_{ij} represents the observed probability of that combination among all mosaic flies, and $\sum a_{ij} = 1$. The antidiagonal cases are those in which the dividing line separates A and B. If the blastula surface is covered half with normal and half with mutant cells, and the dividing lines fall randomly on the surface, a_{11} and a_{00} should be equal, and a_{10} and a_{01} should be equal. This is indeed the general rule for the experimental data^{5,15,16}. If the egg is bilaterally symmetric, the data for one side of the embryo should be the same as for the other. This too is observed. Hence, the data on both sides may be pooled, yielding $2N$ observations for N mosaic flies. The map distance between the sites is $AB = a_{10} + a_{01}$. The distance of a third site C from A and from B can now be measured in the same way (Fig. 4). Extension to additional landmarks, measured two by two, leads to construction of a two-dimensional map that corresponds to the relative positions of their primordial sites on the blastula surface. Garcia-Bellido and Merriam⁵ did this using Sturtevant's data on 379 mosaics of *Drosophila simulans*. A similar map for the thorax of *Drosophila melanogaster* has been constructed by Ripoll¹⁵. Fig. 5 shows our own map based on 703 gynandromorphs of *Drosophila melanogaster*. The distance between any two sites is indicated in *sturts*, one unit representing a probability of 1% that, among the entire set of adult mosaics (formed by this method), the two structures in question will be of different type. Along with Dr John Merriam, we propose this unit in memory of A. H. Sturtevant who was known as "Sturt" to his colleagues and friends.

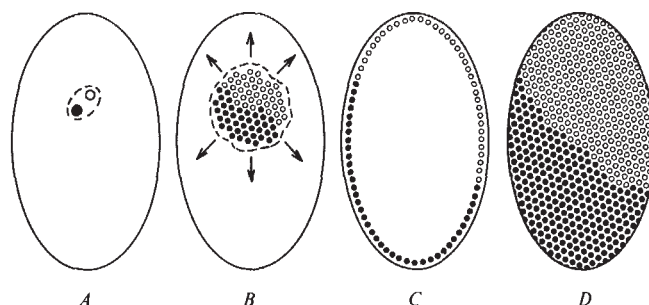


Fig. 3 Formation of a mosaic fly by loss of one X chromosome. Initial egg is female containing a ring X chromosome (X_R) plus a second X chromosome (X^*) carrying recessive genes for marking the body surface as well as the behavioural character to be studied. X_R is lost in about 35% of X^*X_R eggs at first division of the zygote nucleus (A) producing one X^*X_R nucleus (solid circle) and one X^*O nucleus (open circle). Nuclei divide in cluster (B) then migrate to egg cortex, where cell membranes form to produce a blastoderm one cell thick (C). D shows the surface as seen from outside; part of the blastoderm area is covered by each cell type; the mosaic boundary separates the two areas. This is a simplified sketch. For details on embryology see Sonnenblick¹⁰; for mechanism of ring X loss, see Hinton⁸.

The map distances observed are not exactly additive because, with large distances the probability increases that a boundary, having once intersected the line connecting the two sites, will cross back again, and both sites end up with the same genotype. This decreases the apparent value of large distances in analogy to the effect of double crossing over in genetic mapping. The true distances between widely separated points are most accurately obtained by summation of small intervals. Another source of distortion of the map is, of course, the fact that the convex egg surface is represented on a flat sheet of paper. The map shown in Fig. 5 is for the right half of the blastoderm, as seen from inside the egg. The area shown produces the right half of the animal; a symmetrical half-blastoderm produces the left side. For homologous landmarks A and A' on opposite sides to be different in genotype, the mosaic boundary must pass between the two corresponding sites, that is, must intersect a line joining them across the midline. Thus, the percentage of mosaic flies in which A and A' are of opposite sex represents twice the (arc) distance between either site and the midline. In Fig. 5, the distances to the midline are indicated by dotted lines. The outline resembles the surface of half a *Drosophila* egg.

The arrangement of adult body parts arising from the various sites is a sort of cubist collage (Fig. 6); later development will involve extensive movement and reorientation of the parts. Much of the area remains unaccounted for, because the blastoderm gives rise to the internal organs of the adult fly, as well as the entire larva, and these are not represented by the externally visible adult landmarks used to construct the map. The outlines of the areas destined to become the nervous system and the mesodermal region due to produce the muscles¹⁷ are shown (dotted lines) in Fig. 6. In what follows, it will be seen that the foci of certain behavioural mutants are located in precisely these areas.

Mapping a Behavioural Focus

In a fly that is mosaic for a behavioural character, that character can be scored as mutant or normal, in the same way as a visible part of the body. One can combine a recessive behavioural gene with surface marker genes on the *X** chromosome, produce mosaics by loss of *X_R* and ask whether the

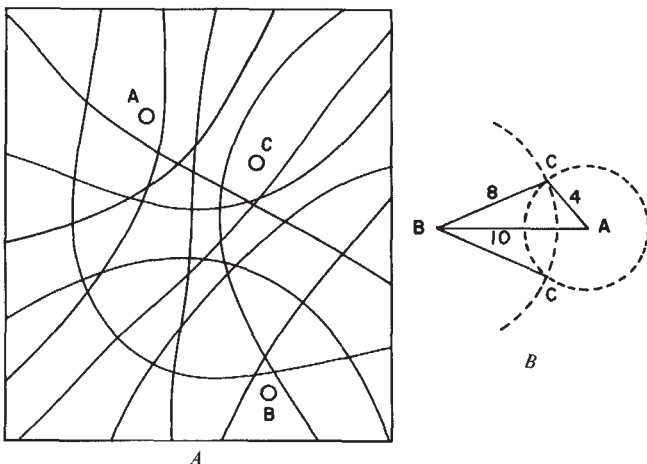


Fig. 4 *A*, Principle of mosaic mapping. Mosaic boundary lines fall in random orientation on the blastoderm. The farther apart two sites are, the more likely it is that the boundary will pass between them. In that event, the corresponding body structures derived from these sites will be of different genotype. By observing the proportion of mosaic flies in which two body structures differ in genotype, a measure of the distance between their embryonic sites is thus obtained. One sturt is defined as a distance such that the boundary line passes between the sites in 1% of the mosaics. *B*, Location of a third site by triangulation. Sites A and B are 10 sturts apart. If site C is 4 sturts from A and 8 sturts from B, then C is located at one of the two intersections. Choice between the two possibilities requires mapping with respect to additional sites.

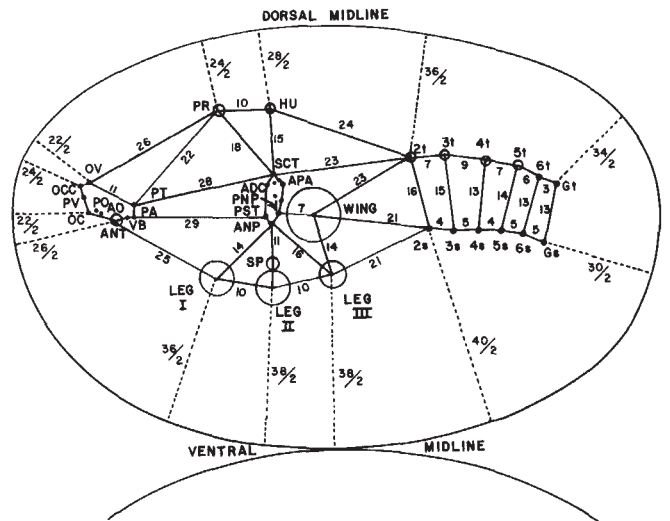


Fig. 5 Fate map of the *Drosophila melanogaster* blastoderm for adult external body parts, constructed by mosaic mapping. The map is a projection of the right half of the blastoderm as seen from inside the egg, showing sites of cells that will eventually develop into the indicated parts of the right side of the fly. A similar map, with mirror symmetry, corresponds to the left side. Distances between pairs of sites are indicated in sturts. Dotted lines indicate distances to the nearest midline, as obtained by halving the distance measured between two homologous contralateral sites. The data are based on scoring of 703 mosaic flies (1,406 sides). The size of circle used to represent a site is proportional to the frequency with which the corresponding structure is itself split by the mosaic boundary.

behaviour exhibited by a mosaic fly corresponds to the same or different genotype as a particular surface landmark. If one is mutant, the other normal, it can be concluded that, in that individual, the mosaic boundary on the blastula passed between the primordial site for the surface landmark and the one for the behavioural focus, that is, the structure in the fly which, when mutant, causes mutant behaviour. By observation of many mosaics, the distance can be obtained, in sturts, from any external landmark to the behavioural focus, which can then be added to the map. This is illustrated below for various behavioural mutants. As the analysis will show, certain behavioural mutations can be assigned to single foci; others require multiple foci for their explanation.

Visual Receptor Mutants

A series of mutants having defective vision and abnormalities in the electrical response of the eye (ERG), involving five

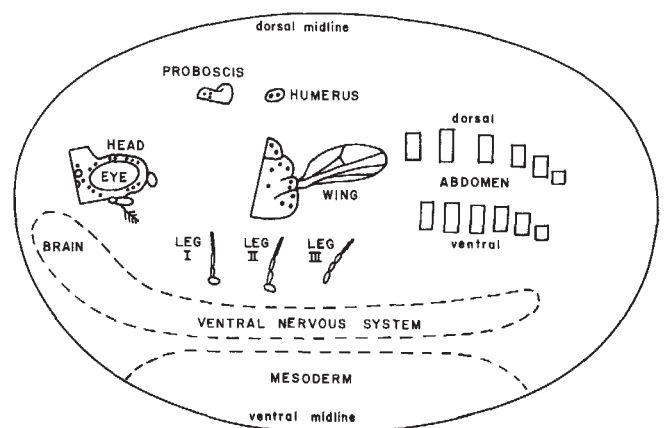


Fig. 6 Pictorial sketch of the external parts of an adult fly derived from various sites on the blastoderm, based on the fate map. This represents only the right half of the fly; the left parts are formed from the other half of the embryo. Dotted lines indicate areas which, according to embryological studies, give rise to the nervous system and the mesoderm.

different genes on the *X*-chromosome, was studied in mosaics¹, the genotype of the eye being tagged by colour genes. Every mutant eye produced a mutant ERG, while genetically normal eyes functioned normally (Table 1). Thus, the blastoderm cells giving rise to the eye were never separated by the mosaic boundary from those responsible for the visual deficit. The mutant foci therefore map at or very close to the eye itself, that is, within the area of Fig. 5 bounded by the orbital bristles.

Table 1 Electroretinogram vs Eye Genotype in 217 Flies Mosaic for five ERG Defect Genes (pooled data)

A, Data for each combination of left and right eyes				
ERG	Genotype of each eye			
	L, normal; R, normal	L, normal; R, mutant	L, mutant; R, normal	L, mutant; R, mutant
L, normal; R, normal	30	0	0	0
L, normal; R, mutant	0	49	0	0
L, mutant; R, normal	0	0	60	0
L, mutant; R, mutant	0	0	0	47

B, Combined data for all eyes		
ERG	Eye genotype	
	Normal	Mutant
Normal	169	0
Mutant	0	203

Table 2 Mapping of Focus for Shaking Behaviour of Leg I in Flies Mosaic for the Hyperkinetic Gene *Hk*¹

Shaking of leg I	A, Coxa of leg I		B, Coxa of leg II		C, Coxa of leg III	
	Normal	Mutant	Normal	Mutant	Normal	Mutant
Normal	277	50.5	261.5	69	250.5	82.5
Mutant	33	223.5	44	215.5	46.5	215.5

Shaking of leg I	D, Presutural bristle		E, Antenna (segs 1, 2)		F, Humeral bristles	
	Normal	Mutant	Normal	Mutant	Normal	Mutant
Normal	251	84.5	253	82	241	94
Mutant	42	222.5	84.5	179.5	66.5	197.5

G, Shaking of right leg I		
Shaking of left leg I	Normal	Mutant
	Normal	110.5
Mutant	59.5	75

Each matrix gives number of each combination observed among 300 mosaic flies examined. Data for right and left sides are combined, making a total of 600 sides.

"Normal" shaking refers to the small amplitude typical of heterozygous flies. In cases where a body structure is mosaic or where amplitude of shaking is intermediate, a value of 1/2 is assigned to each of the two corresponding categories. Those rare cases (a few per cent) where both structure and shaking amplitude are mosaic are omitted.

Calculation of map distances:

$$A, \text{Shaking of leg I to coxa of leg I} = \frac{83.5}{600} = 13.9 \text{ sturts}$$

$$B, \text{Shaking of leg I to coxa of leg II} = \frac{113}{600} = 18.8 \text{ sturts}$$

$$C, \text{Shaking of leg I to coxa of leg III} = \frac{129}{600} = 21.5 \text{ sturts}$$

$$D, \text{Shaking of leg I to presutural bristle} = \frac{126.5}{600} = 21.1 \text{ sturts}$$

$$E, \text{Shaking of leg I to antenna} = \frac{166.5}{600} = 27.8 \text{ sturts}$$

$$F, \text{Shaking of leg I to humeral bristle} = \frac{160.5}{600} = 26.8 \text{ sturts}$$

$$G, \text{Shaking of left leg I to shaking of right leg I} = \frac{108.5}{300} = 36.2 \text{ sturts}$$

$$\text{Distance of leg I shaking focus to midline} = \frac{36.2}{2} = 18.1 \text{ sturts}$$

This eliminates the possibility that some distant organ is the primary focus altered by gene mutation, causing malfunction of the eye by, say, failure of the organ to produce some circulating substance. A good precedent for such an effect is the eye colour mutation *vermillion*, which is not expressed in mosaics having normal abdominal tissue¹⁸.

Hyperkinetic Mutant

The *Hyperkinetic* gene *Hk*¹ causes shaking of the legs of flies under ether anaesthesia. Ikeda and Kaplan² reported that in flies mosaic for this gene, the shaking property of a leg usually correlated well with its cuticle genotype, but not always. Thus, the external structure of a leg is distinct from its behavioural focus. This would be consistent with their neurophysiological observations¹⁹ that abnormal function of the thoracic ganglion is involved, since the ganglion and the leg originate from different areas of the blastoderm.

600 mosaic flies were produced in which the *X*⁺*X*_R parts were female, had normal body colour, eye colour, and bristles, and were heterozygous for *Hk*¹. The *X*⁺*O* parts were male, had yellow body colour, abnormal eye colour, forked bristles, and were hemizygous for the *Hk*¹ gene, thus showing the shaker effect much more strongly than the heterozygote. Mosaics of all compositions were collected, scored for various surface landmarks and examined under ether for shaking of each leg. It was confirmed that (1) the shaking response of each leg is independent of other legs, (2) the shaking response and the (cuticle) genotype of a leg are usually, but not always, the same.

The independent behaviour of the legs indicates that each has a separate focus. The distance in sturts between the shaking focus of a leg and its cuticle site can be determined as illustrated in Table 2A. Similarly, the distance from the leg I shaking focus to various other surface landmarks can be calculated from Table 2. Repeating the process for the focus of each leg yields three distinct locations (Fig. 7). The distance between the foci of the left and right legs of a homologous pair is obtained by comparing their shaking behaviour (Table 2G). One half of this value is thus the distance from each of the foci to the midline.

Each focus lies nearest to its corresponding leg, but all are ventral to any of the adult cuticular sites and lie in the region of the blastoderm indicated by Poulson as the origin of the ventral nervous system. With the electrophysiological evidence that neurones in the thoracic ganglion behave abnormally in *Hk*¹, this probably identifies parts of the thoracic ganglion on the fate map.

Complex foci: drop-dead

Normal *Drosophila* adults live for weeks under laboratory conditions. We have discovered a new mutant which dies

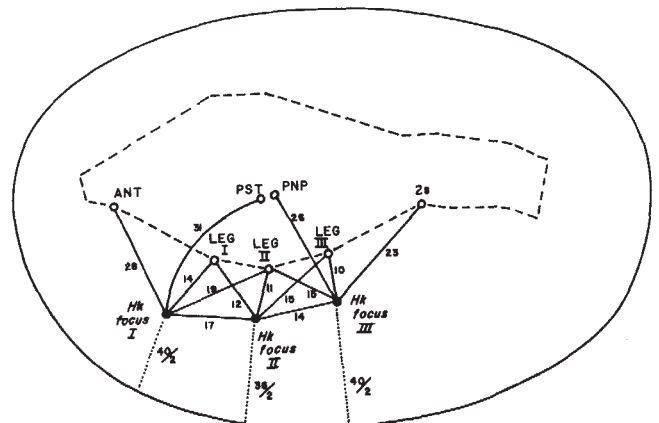


Fig. 7 Fate map sites of the behavioural foci for the hyperkinetic mutant *Hk*¹. There is a separate focus for each leg; they fall in the region of the blastoderm which, according to embryological studies, gives rise to the ventral nervous system.

precociously. These *drop-dead* (*drd*) mutant flies initially develop and behave normally, but at some time an individual begins to walk in an uncoordinated manner, and within a few hours dies. The time of onset of this syndrome varies (Fig. 8). After an initial lag, the number of survivors drops exponentially with a half-life of about 2 days, survivors continuing to behave normally until the abrupt onset of symptoms. It is as if some random event triggers a cataclysm. The gene is recessive, located on the *X* chromosome between *vermillion* and *forked*, and has complete penetrance; virtually all mutant individuals die long before any mortality occurs in normal flies. The death rate of *drd* flies changes little with temperature from 18° to 29° C and is similar for hemizygous males and homozygous females.

A priori, symptoms such as these could result from malfunction in almost any part of the body of the fly, such as blockage of the gut, a general biochemical disturbance, or a nervous disorder. To localize the defective focus, 403 mosaics were made whose *X*O* body parts were hemizygous for *drd* and surface markers, and whose *X*X_R* parts were heterozygous and, therefore, normal for these characters. All the mosaics were scored for *drop-dead* behaviour and for the genotypes of the various body landmarks.

To localize roughly the *drop-dead* focus, it is helpful first to determine whether it is nearest to the head, thorax or abdomen. For this purpose, consider only flies in which the cuticle of any of these structures is solidly of either mutant or normal type. The results are summarized in Table 3. Among mosaics in which the entire head surface was normal, the great majority showed normal behaviour, surviving for 15 days or more. But six flies out of the ninety-seven in this class died, displaying typical *drop-dead* symptoms. In the reciprocal class, eight flies, out of eighty having entirely mutant head cuticles, lived. Thus, the area of the blastoderm giving rise to the part of the fly responsible for the *drop-dead* effect is close to, but distinct from, the area giving rise to the head surface. It lies in such a position that there is a probability of 8% that a mosaic dividing line will pass between it and an envelope which entirely surrounds the areas defining the two sides of the head cuticle. The distances from the thorax and abdomen are much larger: 16 and 38 sturts, respectively.

The problem can be examined further by looking at individuals with mosaic heads. In the case of the ERG mutants, the ERG defect was always observed in the eye on the mutant side

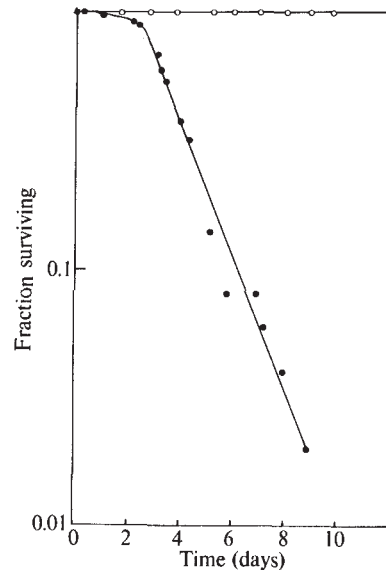


Fig. 8 Survival curve of *drop-dead* mutant males (●) and normal (C-S) males. Temperature=23° C.

of the head; results for mosaics with head cuticle entirely normal, half-normal, or all-mutant were symmetrical. For *drd*, the result is quite different; as shown in Table 3D, symmetry breaks down. Of mosaics in which half the head surface was mutant, only about 17% behave as typical *drop-dead* mutants, while 83% survive for at least 14 days.

This asymmetry presents a new problem. A given internal part should occur in mutant or normal form with equal probability, as is true for the external parts. If there were a single focus in the head for the *drd* gene, therefore, half the bilateral-mosaic flies should drop dead, which is not the case. Suppose instead that there are two foci, one on each side, such that *both* must be mutant in order for the syndrome to appear. On this model, if an individual shows the *drop-dead* phenomenon, both foci can be concluded to be mutant, but for flies that survive, it can only be said that either or both foci are normal. Locating dual foci on the fate map requires special analysis.

Mapping Interacting Foci

In mapping a bilateral pair of interacting foci, two simple possibilities will be considered. Case (1): mutant behaviour results only when both symmetrical foci are mutant, that is, a mutant focus is "submissive" to a normal one. Case (2): one mutant focus is sufficient, that is, a mutant focus is "domineering" with respect to a normal one. When a mosaic dividing line falls between the two foci, the result in the first case is

Table 3 Preliminary Mosaic Mapping of *drop-dead* Behavioural Focus

A, Head matrix		Entire head cuticle	
Survival behaviour		Normal	Mutant
Normal		91	8
Drop-dead		6	72
Distance of focus from head = $\frac{14}{177} = 8$ sturts *			
B, Thorax matrix		Entire thorax cuticle	
Survival behaviour		Normal	Mutant
Normal		51	12
Drop-dead		6	47
Distance of focus from thorax = $\frac{18}{116} = 16$ sturts			
C, Abdomen matrix		Entire abdomen cuticle	
Survival behaviour		Normal	Mutant
Normal		54	28
Drop-dead		23	31
Distance of focus from abdomen = $\frac{51}{136} = 38$ sturts			
D, Behaviour of flies with bilaterally mosaic heads.			
Normal	19 ;	Drop-dead	4

* Strictly speaking, these are not proper sturt units, because the calculation is not based on the entire ensemble of mosaics. However, this usage is acceptable as a preliminary measure.

Table 4 Probability of a Mosaic Fly of a Particular Type

A, Surface landmarks A and A'			
Internal foci f and f'	Both sides normal	One side normal, one mutant	Both sides mutant
Both normal	p_4	p_3	p_1
One normal, one mutant	p_2	p_5	p_2
Both mutant	p_1	p_3	p_4
B, Surface landmarks A and A'			
Behavioural character	Both sides normal	One side normal, one mutant	Both sides mutant
Normal	a_{11}	a_{10}	a_{00}
Mutant	b_{11}	b_{10}	b_{00}

A, Any part is equally likely to occur as mutant or normal, so these probabilities are symmetric around the centre (p_2). Since the internal foci cannot be scored directly, not all of these classes are experimentally distinguishable. The table thus degenerates to B, where a_{ij} and b_{ki} represent the number of mosaic flies of each observable group.

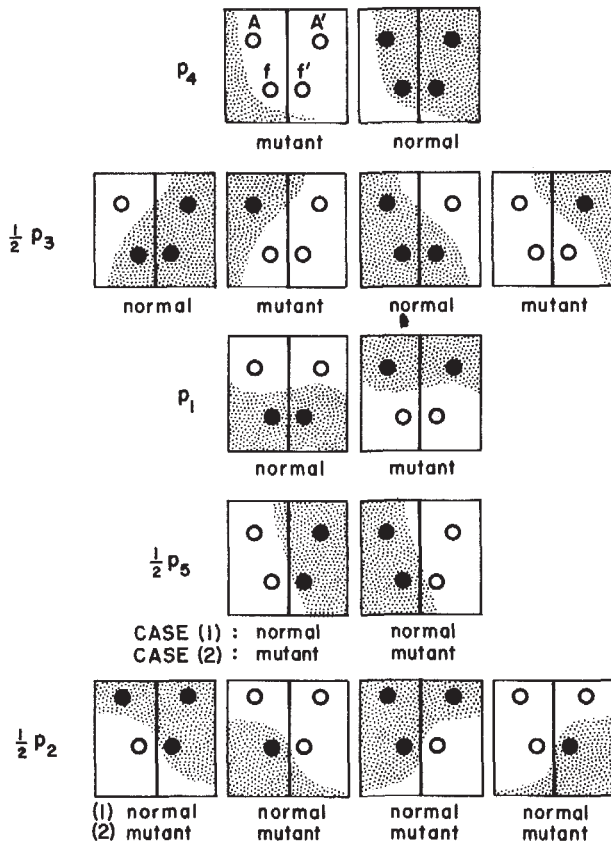


Fig. 9 Various configurations of the mosaic boundary with respect to sites determining a bilaterally homologous pair of surface landmarks (A, A') and a pair of behavioural foci (f, f'). One side of the boundary is covered by normal cells (shaded), the other by mutant cells. The probability (p_i) of each configuration depends on the relative locations of the sites and foci. The behaviour expected is given below each diagram. When the boundary falls between the two foci, the resultant behaviour depends on whether a mutant focus is submissive to a normal one, so that both foci must be mutant to produce mutant behaviour (case 1), or whether a mutant focus is domineering toward a normal one, so that mutant behaviour results if either or both foci are mutant (case 2). Two of the sixteen theoretically possible combinations are omitted, namely, the one where A and f' are mutant and the one where A' and f are mutant. These require multiple crossings of the dividing line between the sites and would be expected to be very infrequent, particularly when the sites and foci are close together.

normal behaviour, in the second mutant behaviour. Fig. 9 shows the various possible mosaic types involving a homologous pair of surface landmark sites (A and A') and a symmetrical pair of internal foci (f and f'); p_i is the probability that the configuration will be of the specified type. These probabilities may be tabulated as in Table 4.

The problem is to determine the p values from these observable frequencies. Consider case (1), where the mutant character is expressed only when both foci are mutant. Mosaics in which the dividing line passes between the two behavioural foci (two bottom rows in Fig. 9) will all exhibit normal behaviour. From case-by-case inspection of Fig. 9: Sum of probabilities: $2p_1 + 2p_2 + 2p_3 + 2p_4 + p_5 = 1$. Probability that dividing line passes between A and A':

$$\overline{AA'} = \frac{a_{10} + b_{10}}{\text{total number of mosaic flies}} = 2p_3 + p_5$$

Among mosaics with A and A' normal, the proportion that show mutant behaviour:

$$\frac{b_{11}}{a_{11} + b_{11}} = \frac{p_1}{p_1 + p_2 + p_4}$$

Among mosaics having A and A' of different genotype, proportion that show mutant behaviour:

$$\frac{b_{10}}{a_{10} + b_{10}} = \frac{p_3}{2p_3 + p_5}$$

Among mosaics having A and A' mutant, proportion that show mutant behaviour:

$$\frac{b_{00}}{a_{00} + b_{00}} = \frac{p_4}{p_1 + p_2 + p_4}$$

These are five equations with five unknowns, and the solutions are:

$$p_1 = \frac{1}{2} (1 - \overline{AA'}) \left(\frac{b_{11}}{a_{11} + b_{11}} \right)$$

$$p_2 = \frac{1}{2} (1 - \overline{AA'}) \left(\frac{a_{11}}{a_{11} + b_{11}} - \frac{b_{00}}{a_{00} + b_{00}} \right)$$

$$p_3 = \overline{AA'} \left(\frac{b_{10}}{a_{10} + b_{10}} \right) \quad p_4 = \frac{1}{2} (1 - \overline{AA'}) \left(\frac{b_{00}}{a_{00} + b_{00}} \right)$$

$$p_5 = \overline{AA'} \left(\frac{a_{10} - b_{10}}{a_{10} + b_{10}} \right)$$

The distance $\overline{AA'}$ between the surface landmarks can be obtained either from the original fate map data or from these data as $a_{10} + b_{10}$ divided by the total number of mosaic flies. The map distance $\overline{Af}$ between site A on one side and the ipsilateral focus corresponds to the frequency with which the boundary passes between them. From Fig. 9 this is:

$$\overline{Af} = 2p_1 + p_2 + p_3 = \frac{1}{2} (1 - \overline{AA'}) \left(\frac{a_{00}}{a_{00} + b_{00}} + \frac{b_{11}}{a_{11} + b_{11}} \right) + \overline{AA'} \left(\frac{b_{10}}{a_{10} + b_{10}} \right)$$

Similarly, the distance between the two behavioural foci:

$$\overline{ff'} = 2p_2 + p_5 = (1 - \overline{AA'}) \left(\frac{a_{11}}{a_{11} + b_{11}} - \frac{b_{00}}{a_{00} + b_{00}} \right) + \overline{AA'} \left(\frac{a_{10} - b_{10}}{a_{10} + b_{10}} \right)$$

Half the value of $\overline{ff'}$ defines the distance between each focus and the midline. Various different landmarks (As) may be used for calculating the positions of the submissive foci; consistency of the results provides a check on the method. Case (2) for domineering foci may be handled in similar fashion, as will be discussed later, in connexion with *wings-up* mutants.

Mapping the Foci of *drop-dead*

Table 5 gives the relevant data on *drop-dead* mosaics, and illustrates our method of calculation. The resultant map position of one of the *drd* foci (that on the right side of the embryo) is indicated in Fig. 10. This focus is ventral to the head cuticle area, in a position that suggests the brain as the primary site.

Table 5 Mapping of the *drop-dead* Foci with Respect to a Pair of Surface Landmarks, based on the Two-focus Model, for 403 Mosaic Flies

Survival behaviour	Left and right ocellar bristles (A and A')		
	Both sides normal	One side normal, one mutant	Both sides mutant
Normal	160	51	19
Mutant	13	28	132

Calculations:

$$\overline{AA'} = \frac{51 + 28}{403} = 19.6 \text{ sturts}$$

$$p_1 = \frac{1}{2} \left(1 - \frac{51 + 28}{403} \right) \left(\frac{13}{160 + 13} \right) = 0.030$$

$$p_2 = \frac{1}{2} \left(1 - \frac{51 + 28}{403} \right) \left(\frac{160}{160 + 13} - \frac{132}{19 + 132} \right) = 0.021$$

$$p_3 = \left(\frac{51 + 28}{403} \right) \left(\frac{28}{51 + 28} \right) = 0.069$$

$$p_4 = \frac{1}{2} \left(1 - \frac{51 + 28}{403} \right) \left(\frac{132}{19 + 132} \right) = 0.351$$

$$p_5 = \left(\frac{51 + 28}{403} \right) \left(\frac{51 + 28}{51 + 28} \right) = 0.057$$

$$\bar{A}f = 2p_1 + p_2 + p_3 = 15.0 \text{ sturts} \quad \bar{f}f' = 2p_2 + p_5 = 9.9 \text{ sturts}$$

Indeed, histology of *drop-dead* flies, fixed at the stage where staggering has set in, shows striking degeneration of the brain²⁰. Mutant flies fixed before the onset of symptoms showed apparently normal histology. Among bilateral mosaics, in which half the head cuticle was normal, the other half mutant, half the brain would be expected, on the average, to be composed of mutant cells. Of thirty such flies studied, eight developed *drop-dead* symptoms within 10 days while twenty-two survived (for more than 14 days). All the affected flies showed degeneration of the brain on both sides, while the surviving flies showed no degeneration on either side. This is consistent with the model requiring two symmetric foci, both of which must be mutant for degeneration to occur. The absence of any histologically asymmetric cases, among the thirty bilateral mosaics examined, suggests that one normal side of the brain may supply some factor, conceivably of neuro-endocrine nature, which prevents deterioration of the other.

Bilateral Domineering Foci: *wings-up*

We have isolated a mutant called *wings-up A* (*wup A*) which raises both wings vertically soon after emergence, and maintains them permanently in that position. The mutant cannot fly, but behaves normally in other respects. The phenotype is expressed in all hemizygous males and 95% of homozygous females. The gene is on the *X* chromosome, to the right of *forked*. It is recessive; in heterozygotes, wing position and flight are normal. In a second *wings-up* mutant (*wup B*) which resembles *wup A* in appearance, a different gene is involved, located on the *X* chromosome between *vermillion* and *forked*. The *wup A* and *wup B* genes complement to produce normal behaviour. The heterozygote of *wup B* holds its wings in normal position, but does not fly. Thus, the flightless behaviour caused by this gene is dominant, while the wing position abnormality is recessive.

The *wings-up* syndrome could conceivably result from a defect in the wing, its articulation, the controlling muscles, neuromuscular junctions, or the central nervous system. The mosaic technique can be used to distinguish between these possibilities. We made 191 mosaic flies in which the *X*O* parts carried *wup A* (and other markers), while the *X*X_R* parts were normal. Among them, 113 held both wings up and 78 held both wings in normal position. 359 mosaics were made in which the *X*O* parts carried *wup B*, while the *X*X_R* parts were heterozygous for *wup B*. Among them, 210 held both wings up and 147 held both wings at normal position. Six flies were unusual; they held both wings in a drooped-down position which is not seen among either wild-type or mutant flies. The striking fact, for both mutants, is that the position of both wings was always the same, even for bilaterally mosaic flies.

For preliminary mapping, mosaics were scored for separation of the head, thorax or abdomen genotype from the *wings-up* character (Table 6) and the foci for both mutants were found to be far from the head and the abdomen, but near the thorax. They are separable from the thorax cuticle, however; some flies occur in which the wings are held up, even though the entire external thorax, including the wings themselves, is of normal genotype. This immediately excludes the possibility that the wing or its articulation is the focus and suggests, instead, that some structure inside the thorax may be involved.

Table 6 Preliminary Mosaic Mapping of *wings-up* Behavioural Foci

		<i>wup A</i> mutant		<i>wup B</i> mutant	
A, Head matrix		Entire head cuticle			
Wing position		Normal	Mutant	Normal	Mutant
Normal		27	12	79	21
Up		11	45	50	84
Distance of focus from head:		24 sturts		30 sturts	
B, Thorax matrix		Entire thorax cuticle			
Wing position		Normal	Mutant	Normal	Mutant
Normal		15	1	44	1
Up		1	35	6	52
Distance of focus from thorax:		4 sturts		7 sturts	
C, Abdomen matrix		Entire abdomen cuticle			
Wing position		Normal	Mutant	Normal	Mutant
Normal		17	4	31	11
Up		8	8	45	36
Distance from abdomen:		32 sturts		46 sturts	
D, Behaviour of flies with bilaterally mosaic thorax					
Wing position					
Normal		13		11	
Up		19		19	

Unlike *drop-dead* mutants, a majority of the mosaics shows mutant behaviour, holding both wings up. This suggests two bilateral foci, a mutant focus being domineering with respect to a normal one; if either (or both) of the foci is of mutant type, both wings will be held up. This is case (2) referred to above, and the behaviour expected for various configurations of the dividing line is given in Fig. 9. The derivation of the probability of each mosaic class from the observed data can be done in a manner analogous to case (1), the solutions becoming:

$$\bar{A}f = \frac{1}{2} (1 - \bar{A}A') \left(\frac{a_{00}}{a_{00} + b_{00}} + \frac{b_{11}}{a_{11} + b_{11}} \right) + \bar{A}A' \left(\frac{a_{10}}{a_{10} + b_{10}} \right)$$

$$\bar{f}f' = (1 - \bar{A}A') \left(\frac{b_{00}}{a_{00} + b_{00}} - \frac{a_{11}}{a_{11} + b_{11}} \right) + \bar{A}A' \left(\frac{b_{10} - a_{10}}{a_{10} + b_{10}} \right)$$

Using these equations, the positions of the *wup A* and *wup B* foci were calculated. Both mapped to the same region, shown in Fig. 11. These foci lie close to the ventral midline. According to embryological observations, this area invaginates to produce the mesoderm, which suggests that a muscle defect may be responsible for *wings-up* behaviour.

Indeed, the abnormality in the mutant becomes obvious

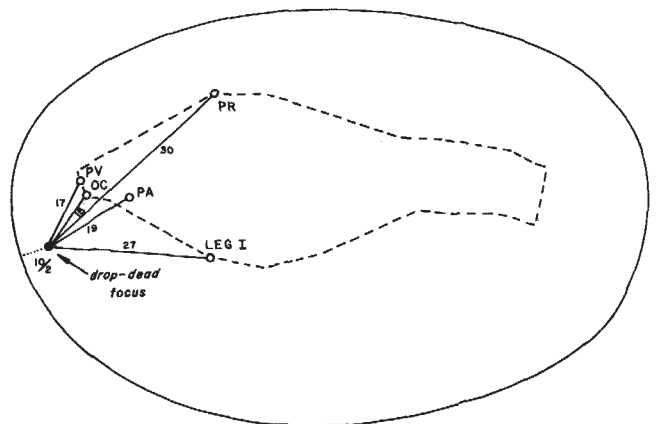


Fig. 10 Fate map of the *drop-dead* mutant focus.

when the thorax is dissected in Ringer solution and the indirect flight muscles are examined under phase contrast. Normal *Drosophila* flight muscle²¹ shows regularly banded myofibrils and many mitochondria. In *wup A*, the flight muscles are atrophic; in *wup B*, the muscle fibre envelopes are present and filled with mitochondria, but the myofibrils are almost entirely lacking. These observations apply to both the longitudinal and the vertical fibrillar type indirect flight muscles which alternately compress the thorax, supplying power to the wings during flight^{22,23}. Other muscles, of the tubular type, such as the leg muscles or direct wing muscles, appear quite intact; both mutants walk and climb normally. In flies heterozygous for the *wup A* gene, the muscles (and flight behaviour) are quite normal. *wup B* heterozygotes, on the other hand, hold their wings in normal position, but do not fly. Electron microscopy shows that the flight muscles of the latter are defective; while thick and thin filaments are arranged in the normal hexagonal array, the Z-line is often crooked and sometimes forked, in contrast to normal indirect flight muscle, where the Z-lines run straight across the fibril.

In normal flies, the indirect flight muscles develop during metamorphosis from myoblasts aligned along larval thoracic muscles^{24,25}. A group of myoblasts fuses to form a multinucleate cell, whereupon the characteristic filaments appear and associate into bundles to form the myofibrils. Histological examination of *wup A* at various stages showed that the formation of indirect flight muscle proceeds normally throughout most of pupal life, but the muscles then degenerate; in the two-day-old adult, little remains of the structure. In the heterozygote, one normal gene is sufficient to prevent this degeneration. In *wup B*, myoblasts appear in normal numbers and fuse, but bundles of filaments, which normally appear at two days of pupal age, fail to appear in the mutant. It is conceivable that the *wup B* mutant fails to synthesize (or synthesizes incorrectly) some molecule essential to organization of myofibrils, for example, a component of the Z-band. The erratic structure in heterozygotes may be due to an inadequate supply of normal molecules.

Twenty-eight flies mosaic for these genes were chosen in which the mosaic boundary ran longitudinally down the middle of the thorax cuticle and were examined histologically. In many cases, some of the indirect flight muscle fibres on either or both sides were abnormal or absent, while others were normal, the internal dividing line varying in each case. The various muscle fibres appeared to be essentially independent. In some cases, the boundary passed through a single fibre, so that one end was normal, the other end defective, as to be expected from the fact that each fibre is a multinuclear syncytium. Every mosaic fly with *wings-up* behaviour showed one or more fibres degenerate or missing, sometimes on only one side; no fibres were seriously deficient in any of the flies that had normal wing position. These observations are consistent with expectation from the model assuming a bilateral pair of domineering foci. The behaviour displayed by the wings is a result of the architecture of the thorax. Contraction of the thorax by the vertical indirect muscles causes both wings to snap up, while alternating contraction of the longitudinal indirect muscle brings them down^{22,23}. When both sets of muscles are defective, as in the mutants, the natural state of the thorax apparently corresponds to the *wings-up* position. This occurs also when the muscles on only one side are deficient, as in mosaics. Some of the mosaics that held wings in an unusual down position were also examined. In most cases, the longitudinal muscles were characteristic of the heterozygote, while the vertical muscles were of mutant type, which would account for their behaviour.

Validity of the Mapping Postulates

It was assumed that the mosaic boundary is oriented randomly, separating the blastoderm area into approximately equal halves. Given the various structural sites and behavioural

foci now available on the map, it is possible to make a check on those assumptions by drawing, for a particular mosaic, how the boundary falls. The examples in Fig. 12 illustrate this, showing the external appearance of each fly together with a map boundary consistent with the surface structures and the behaviour observed. In Fig. 12A, the map surface is divisible into roughly equal normal and mutant areas. Because the number of sites and foci is limited, the line is not uniquely determined; it is merely drawn in a plausible way. Fig. 12B calls for the line to be drawn quite differently, and Fig. 12C is for a bilateral mosaic. The fly in Fig. 12D seems, from its surface, to be a patchwork affair. This is an illusion due to the method of assembly of the exoskeleton; the pattern can be accounted for by an embryonic map divided in a simple manner. Of 150 mosaics plotted out in this way, the great majority (90%) were found to be consistent with the basic assumptions. Exceptions are to be expected if some mosaics arise from loss of the X_R chromosome, not at the first nuclear division, but at a later one, so that less than half of the blastoderm is X^*O . Conversely, loss may sometimes occur at the first division and again at a later one, producing an embryo that is more than half X^*O . These relatively rare instances have only a small effect on the mapping data, which are based on the entire ensemble of mosaics. For mosaics made by other methods, using somatic crossing over, or chromosomes that tend to be lost at later stages of development, the sizes of mutant patches may be much smaller, on the average, than half the embryo. The mapping data with such mosaics, for close landmarks, can be made comparable to sturts, as defined here, by normalizing the apparent distance observed to the probability that any landmark is of mutant (or recombinant) type¹⁶.

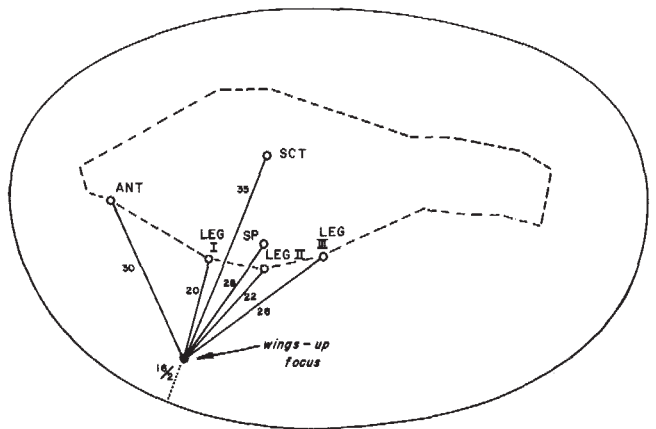


Fig. 11 Fate map of the *wings-up B* mutant focus.

The mosaic boundary is necessarily jagged, because it is formed by a finite number of blastoderm nuclei. Some mixing near the boundary is also bound to occur. The fact that a self-consistent map can be constructed indicates that such mixing is not prohibitively large. However, it certainly does occur on a finer scale, as shown by cell-lineage studies in mosaics produced by somatic crossing over, where clones show varied shapes²⁶.

The mapping procedure assumes that the site at which a nucleus lands on the blastoderm decides its fate. This says nothing about the time at which the determination of a cell to form a specific tissue becomes irreversibly established, which could happen later in development. All that is needed for fate mapping to work is that the cells be constrained by their relative positions in such a way that position on the

blastula becomes tantamount to ultimate identity. If the fate map were inscribed on the egg cortex in fine grain, then the fact that the number of cells forming the blastoderm is limited would place no lower bound on meaningful map distances; the probability that two adjacent blastoderm cells cover different sites or not would depend only on the distance between the sites. Suppose, on the other hand, that the grain is rather coarse, so that a site on the map represents the centre of a distribution function for the probability that cells in the area will eventually give rise to a particular structure. Indeterminacy of this sort would cause the apparent distance between two overlapping areas to be larger than the true distance between their centres, the extra apparent distance being approximately the sum of the standard deviations for the two distributions.

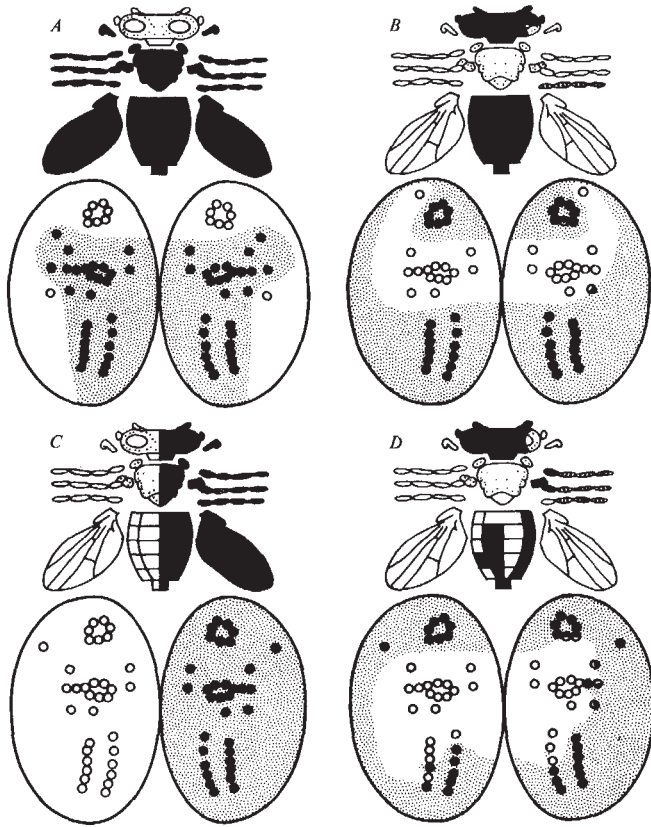


Fig. 12 Orientations of the boundaries in four mosaic flies, deduced from the genotypes of body landmarks and behavioural foci. Dorsal view. Solid circles denote normal sites, open circles denote mutant ones. A plausible dividing line is drawn in each case.

Structures that are produced by a single somatic cell, such as the bristles, make ideal landmarks, but within larger landmarks, mosaicism is often seen. Given a site of circular shape and diameter d sturts, the frequency with which a random mosaic boundary splits the circle can be shown to be $\pi d/2$. Scoring a split landmark as $1/2$ of a mutant case and $1/2$ of a normal case has the effect of placing the site at roughly the centre of the area producing the landmark structure.

The relation of map units to physical distance may not be uniform over the map, since the egg is not spherical. As in mapping genes by recombination, calculated distances may not correspond to physical dimensions, yet this does not interfere with the establishment of linear order. Fate mapping is analogous, but projects to a two-dimensional surface. The essential point in both cases is that topological relationships are preserved.

The mutants used were chosen in order to establish the methodology for mapping intangible characters. Although they involve rather primitive aspects of behaviour, they provide examples concerning sensory receptors, the central nervous system, and the muscles, and thus tell us where these relevant structures are located on the map. Experiments in progress indicate that the same approach can be applied to more elaborate behavioural phenomena such as circadian rhythms^{27,28} and sexual behaviour²⁹. It may be anticipated that complex results may be obtained in some cases. Imagine, for example, a mutant having a defect in a function essential throughout the nervous system, such as generation of action potentials. This would not map to a single focus. Yet the anomalies of mapping would indicate the outlines of the relevant areas.

In some of the mutants described here, histological examination has revealed obvious lesions. One might ask whether the fate mapping was not therefore unnecessary. It is important to stress that, in addition to indicating where in the organism to look for a lesion, the method identifies the primary focus of the mutant gene. That this turns out in some cases to correspond to the tissue related to the mutant behaviour is reassuring, but it must be anticipated that this will not always be so. For example, a histological anomaly of flight muscle could conceivably be neurogenic. In such a case, however, the focus would map onto the area of the blastoderm destined to produce the nervous system. For the *wings-up* mutants analysed the fate map places responsibility squarely onto the muscle itself. Since the map refers to the blastoderm, what the procedure in effect accomplishes is to dissect the complex relationship between nerves and muscles in the adult, unravelling them back to an embryonic stage at which they had not yet come together, so that each can be pinpointed separately.

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Biochemical Evidence for the Bidirectional Replication of DNA in *Escherichia coli*

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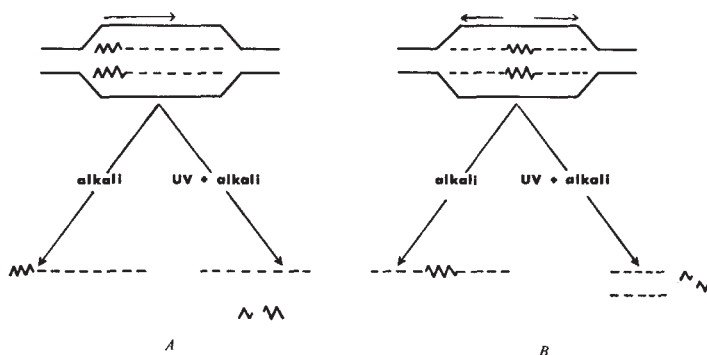
After the initiation of synchronous replication of *E. coli* DNA by a short pulse of BU, BU is found in the middle of the newly synthesized segment confirming bidirectional replication from the origin.

THE chromosome of *Escherichia coli* is a single circular DNA molecule which replicates sequentially¹⁻³ from a fixed origin^{4-14,15}. Although it was initially thought that replication proceeds in a unique direction, Masters and Broda¹⁶ and subsequently Bird *et al.*¹⁷ and Hohlfield and Vielmetter¹⁸ have presented genetic evidence that replication takes place simultaneously in both directions from the origin. We here present confirmatory biochemical evidence that this is so. Since this manuscript was submitted, Prescott and Kuempel¹⁹ have published autoradiographs of bidirectional replication of DNA.

to initiate DNA replication synchronously with the thymine analogue bromouracil (BU) present in place of thymine. BU is then rapidly replaced by ³H-thymine and replication allowed to proceed for a much longer period. The DNA is extracted avoiding degradation of the daughter DNA and divided into two aliquots, one of which is subjected to ultraviolet light to degrade the sections of DNA containing BU, as low doses of ultraviolet light lead to specific breakdown of the sugar-phosphate backbone of DNA adjacent to incorporated BU residues²¹. The newly synthesized radioactive DNA strand segments are separated from the parental DNA strands and analysed with respect to molecular weight, in an alkaline sucrose gradient.

As Fig. 1 shows, if replication is unidirectional (A), BU will be at one end only of each single-stranded segment. As the duration of BU uptake is small compared with that of ³H-thymine, treatment with ultraviolet will make little difference to the size of segments as compared with the untreated control; both should form homogeneous bands in the same region of the sucrose gradient. By contrast, if replication is bidirectional (Fig. 1B), the bromouracil should be located

Fig. 1 Diagrammatic representation of the predicted behaviour of unidirectionally (A) as opposed to bidirectionally (B) replicating origin DNA after the following treatment. Synchronized cells are pulsed for 15 s with 5-bromouracil (---BU-DNA) and then with ³H-thymine for 100 s (---, ³H-DNA; —, unlabelled DNA). Lysates of cultures are either irradiated with ultraviolet light, or left unirradiated, and centrifuged on alkaline sucrose gradients.



Bidirectional Replication of DNA

We adapted to *E. coli* the method with which Weintraub²⁰ demonstrated that DNA replication in developing chick erythroblasts is bidirectional rather than unidirectional. The technique allows one to analyse the way in which the segments of DNA made immediately after initiation of replication are synthesized.

Cells of a thymine-requiring mutant of *E. coli* are allowed

in the middle of each segment, so that treatment with ultraviolet light breaks the segments in two and their molecular weight is approximately halved (see below) as compared with the control. In this case irradiated and unirradiated DNA will appear as separate bands on the sucrose gradient.

Initiation of DNA replication was synchronized in cells of *E. coli* B/r (Thy⁻, Leu⁻, His⁻, Cys⁻, Xyl⁻), growing with a generation time of 40 min on a minimal salts medium, by

allowing them to terminate current rounds of DNA replication while preventing the initiation of new ones, by withholding required amino acids. Thymine was then removed from the medium and amino acids returned to allow synthesis of the proteins required for initiation of replication. Replication was then initiated synchronously by adding BU, which, after 15 s, was replaced with ^3H -thymine for 100 s. Replication was then stopped, DNA extracted, irradiated if required and centrifuged. Fig. 2 shows the difference in sedimentation behaviour of the irradiated and unirradiated extracts: there is a clear shift in molecular weight of the newly synthesized DNA after exposure to ultraviolet. From the positions of the peaks in a series of experiments we have determined²² that the ratio of the molecular weights of the untreated to ultraviolet-treated DNA segments is 2.6 ± 0.3 . This agrees well with the predicted ratio of 2.32 calculated by assuming that all BU moieties will have been removed from the irradiated DNA segments leaving only the thymine-containing DNA. (The fact that increasing the exposure to ultraviolet twenty-fold leads to no further reduction in molecular weight (data not shown) supports this assumption.) The BU incorporated in this experiment therefore behaves as if it were incorporated into the middle of a DNA fragment, as in Fig. 1B, and not as if it were incorporated at its end (Fig. 1A).

By using a mouse satellite DNA fraction of known molecular weight as a standard we calculate that the newly synthesized, ^3H -labelled single-stranded DNA fragments have a molecular weight of 2×10^7 . Assuming that the *E. coli* chromosome has a molecular weight of $1-2 \times 10^9$ and requires approximately 40 min for its synthesis this is about the size of the piece that we would have expected to have been synthesized during the 2 min period of the experiment. The fact that both the irradiated and unirradiated DNAs are homogeneous and of the size predicted, strongly supports the idea that BU is incorporated into the middle of daughter strands of DNA whose replication is bidirectional, and not into a fragment of DNA arising in one of the ways set out below.

BU Found Only in Daughter DNA

The results obtained above, that BU present during the initiation of replication is incorporated internally into a DNA fragment, could have been generated in ways other than that set out in Fig. 1B. According to the model presented there, BU is flanked by ^3H -thymine labelled daughter DNA. By contrast, a number of other models predict that ^3H -thymine would appear only to one side of the BU; the stretch of DNA on the other side of the BU would contain unlabelled thymine. It should be noted, however, that for this to take place a series of coincidences would be required to explain the observed sizes and homogeneity of the fragments described above.

The first way in which this could come about would be if parental DNA were used to prime daughter DNA replication, as in rolling circle^{23,24} and some other²⁵ models of DNA replication. According to these models daughter and parental DNA¹⁶ are covalently linked and so first the BU and then the ^3H -thymine would be incorporated in continuation of high molecular weight parental DNA. If this DNA were to fragment during extraction so as to yield pieces of 2×10^7 molecular weight, some of these pieces could be expected to contain BU sequences flanked by parental and daughter DNA which could behave as described above.

If termination of rounds of chromosome replication did not occur during the synchronization treatment, but only after BU and labelled thymine had been added to the medium, linkage between parental and daughter DNA would also be found. Although Stein and Hanawalt²⁶ and Kuempel (submitted for publication) failed to detect linkage between parental and daughter DNA in *E. coli* 15T⁻ we thought it

essential also to exclude such linkage in B/r under the conditions of our experiment.

Another source of error could be the retention of an internal pool of thymine after termination of rounds of replication or some leakiness in the thymine requirement of the strain used in these experiments. Initiation of synthesis could then occur during the thymine starvation period and the BU, when added, incorporated in continuation of a previously synthesized piece of DNA. If the amount of synthesis occurring before the addition of BU were approximately equal to that which occurs during the later pulse of ^3H -thymine, pieces could be generated which would behave as described above, and unidirectional synthesis mistaken for bidirectional.

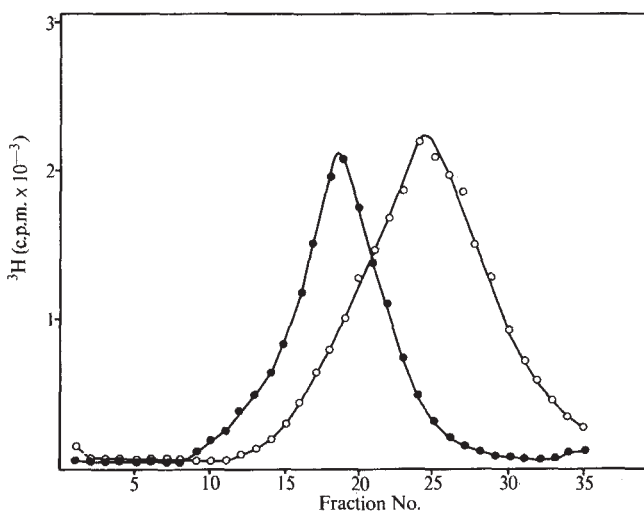


Fig. 2 Centrifugation of irradiated (○—○) and unirradiated (●—●) DNA in which initiation was allowed to take place in bromouracil. 50 ml. cultures at densities of 5×10^8 cells ml^{-1} were synchronized with regard to DNA replication by 100 min of amino acid starvation followed by thymine starvation for one mass doubling time²⁵. The cells were collected on 'Millipore 47 mm HA' membrane filters and washed with prewarmed buffer. The cells were pulsed for 15 s on the filter with 5-bromouracil ($10 \mu\text{g ml}^{-1}$) and washed with prewarmed buffer. Finally, the cells were suspended in 10 ml. M9-glucose+aa+thymine ($1 \mu\text{g ml}^{-1}$)+ ^3H -thymine ($20 \mu\text{Ci } \mu\text{g}^{-1}$). The cells were vigorously aerated for 100 s. DNA replication was stopped and the cells lysed (Fig. 3). In this case 0.2 ml. samples of the crude lysates were exposed to ultraviolet if required (dose 3×10^5 erg) and layered on 5 ml. linear 5–20% alkaline sucrose gradients (0.1 M NaOH, 0.9 M NaCl) for centrifugation in a 'Beckman L2-65B' centrifuge using an SW50.1 rotor at 20,000 r.p.m. for 12 h. Ten drop fractions were collected on 'Whatman 3 MM' paper filters, washed in 5% ice cold TCA followed by 80% ethanol. The samples were counted in PPO-POPOP scintillant (Fig. 3).

We therefore excluded these possibilities by performing an experiment which showed that BU used to initiate replication is not added to a previously synthesized piece of DNA. Bacteria were grown for three generations in a medium containing ^{14}C -thymine to totally label parental DNA. The required amino acids were removed and the cells allowed to terminate rounds of replication in ^{14}C -thymine. After termination thymine was removed, amino acids re-added and incubation continued until all cells were ready to initiate replication. ^3H -bromouracil was then added to the medium and replication allowed to continue for 100 s. The DNA was then isolated and the strands separated and centrifuged on caesium chloride gradients (Fig. 3). The parental ^{14}C -containing DNA is of light density; daughter DNA which is

fully substituted with ^3H -BU is of heavy density. Any DNA stretches which contained both parental and daughter DNA, or BU added to a fragment synthesized during thymine starvation from a retained internal pool, would be doubly labelled and of a density intermediate between that of the thymine containing parental and the BU containing daughter DNA. Fragments synthesized by addition of BU to the unlabelled DNA which could be made during thymine starvation by a leaky mutant using thymine synthesized *de novo* would also be of hybrid density but would not be doubly labelled.

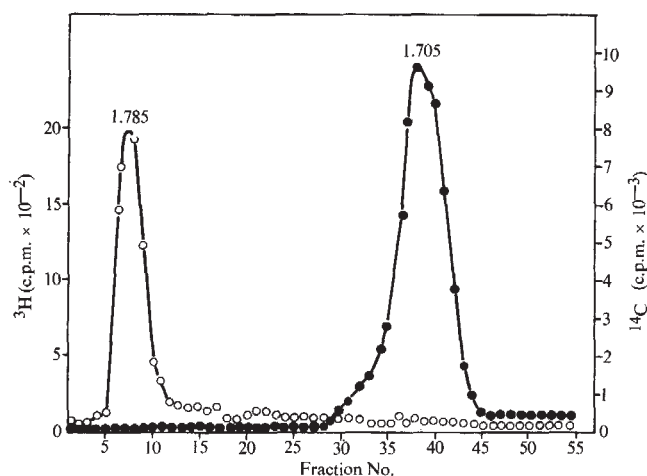


Fig. 3 Separation of daughter and parental DNA on CsCl gradients. *E. coli* B/r (L6) was grown in M9 medium + 0.2% glucose + 10 $\mu\text{g ml}^{-1}$ thymine, 20 $\mu\text{g ml}^{-1}$ each of leucine, histidine and cysteine (aa) with rotary shaking at 37° C. The cells were labelled with ^{14}C -thymine (10^{-2} $\mu\text{Ci } \mu\text{g}^{-1}$) for 3 generations and synchronized by 100 min aa starvation followed by thymine starvation for 1 mass doubling time. The cells were washed with prewarmed buffer and resuspended in M9-glucose + aa + 10 $\mu\text{g ml}^{-1}$ bromouracil + 2 $\mu\text{Ci } \mu\text{g}^{-1}$ ^3H -bromouracil for 100 s and vigorously aerated. DNA replication was stopped in 50 ml. aliquots (5×10^8 cells ml^{-1}) by pouring the cells with crushed ice into buffer B²⁸. After washing twice in $1 \times \text{SSC}$ the cells were suspended in 2 ml. $0.1 \times \text{SSC} + 10^{-3}$ M EDTA and lysed with 1% Na dodecyl sulphate (SDS) + pronase 1 mg ml^{-1} (ref. 29). The DNA lysate was extracted twice with an excess volume of 88% phenol—12% meta-cresol—0.1% 8-hydroxy-quinoline followed by gentle shaking in 24 : 1 mixture of chloroform : octanol to remove the SDS. The DNA was denatured and centrifuged according to the procedure of Stein and Hanawalt²⁶ except that we used 'BDH Analar' grade CsCl and diluted the DNA in 10^{-3} M EDTA. Ten drop fractions were collected into ice cold 5% TCA and counted on 'Whatman' GF/C filters in PPO-POPOP scintillant in a 'Packard Tricarb' liquid scintillation counter. $\circ$, ^3H ; $\bullet$, ^{14}C .

DNA stretches of intermediate density are clearly identifiable when thymine is replaced by BU in the middle of the replicative cycle of *E. coli*²⁷. Fig. 3 gives the data we have obtained from our experiment. No doubly labelled DNA or DNA of intermediate density can be seen. The ^{14}C -DNA bands at 1.705 g cm^{-3} and the ^3H -DNA at 1.785 g cm^{-3} . Assuming that the change in density is proportional to the change in molecular weight these densities are what would be expected on the hypothesis that daughter DNA is fully substituted with BU and neither contains, nor is linked to, light DNA containing thymine. It should be noted that this experiment does not eliminate the possibility that daughter DNA is linked to parental DNA for a period of less than 100 s. Because, however, this is shorter than the labelling period used in the experiment reported above, we conclude that linkage between daughter and parental DNA or between daughter DNA synthesized before and after the addition of BU cannot explain the results in Fig. 2.

Another possible source of error is that BU continues to be incorporated into DNA for some time after it has been replaced in the medium by ^3H -thymine. If BU were simply to compete with thymine for incorporation the result would be stretches of DNA containing both bases which would be expected, on irradiation, to yield many pieces of small size rather than pieces half the size of the initial fragment (Fig. 2). If, however, the BU continued to be incorporated for an appropriate interval to the exclusion of thymine and if replication were unidirectional, pieces could be generated which could be halved in size by the removal of a large number of BU moieties from one end. This could result in our mistaking unidirectional replication for bidirectional.

To eliminate this possibility, initiation was synchronized as described above, replication initiated in BU for 15 s and then the BU replaced with ^3H -thymine. Samples were taken at 10-s intervals and the rate of incorporation of the ^3H -thymine determined. As can be seen (Fig. 4) the thymine is incorporated linearly for at least 8 min after a lag of no more than 10 s indicating that it is not competing for incorporation with a large internal pool of BU. We therefore conclude that the reduction in molecular weight caused by irradiation of the extracted DNA fragments is not a result of their being composed, to a large extent, of bromouracil.

Rolling Circle Model Excluded

Our experiments demonstrate that when cells initiate replication in BU and are subsequently transferred to a medium containing thymine, the BU behaves as if it were contained in the middle of a DNA fragment. As this fragment does not contain any DNA synthesized before the addition of the BU, the BU must be flanked on both sides by the ^3H -thymine-containing DNA made after it had been incorporated. This result is consistent only with bidirectional DNA replication of the sort described in Fig. 1B, in which each daughter strand elongates in both directions from the origin of replication.

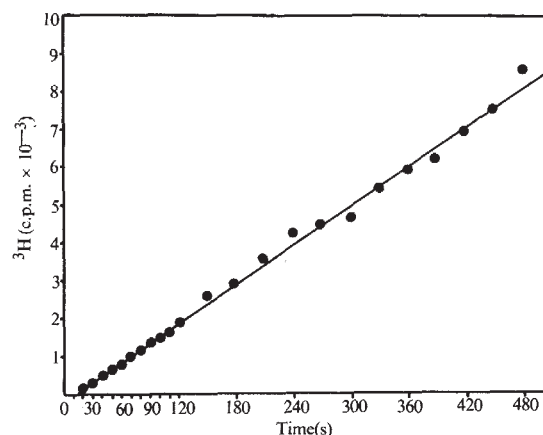


Fig. 4 Thymine incorporation after initiation of replication in BU. Cells were synchronized, labelled with BU and resuspended in ^3H -thymine as described in the legend to Fig. 2. Samples are taken every 10 s for 2 min and then every 30 s for another 6 min into ice cold 7% TCA. TCA precipitates are collected on 'Millipore' filters and counted as described above.

The absence of any linkage between parental and daughter DNA excludes rolling circle and related mechanisms, either uni- or bidirectional, from a role in the vegetative replication of the *E. coli* chromosome.

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Plume Convection with an Upper-Mantle Temperature Inversion

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Convection driven by temperature differences at phase transitions would be accompanied by a temperature inversion below the asthenosphere. The inversion explains the asthenosphere's low viscosity and low velocity.

SOME older inferred barriers to mantle-wide convection, such as chemical zonation, phase transitions, and high lower-mantle viscosities, are being re-examined. Recent inversions of seismic data^{1,2} indicate that although there might be a compositional difference between the upper and lower mantle, a mantle of constant composition is still allowable. Schubert and Turcotte³ have shown that phase transitions can be a dominant driving force behind convection. Lower mantle apparent viscosities, once thought to be in the range of 10^{26} poise, have been revised downward by Dicke⁴. Goldreich and Toomre⁵ showed that the fossil equatorial bulge does not exist, removing one reason for suspecting a high-viscosity lower mantle.

In a major study of responses to post-glacial changes on all scales from the global loading of the oceans down to areas the size of Lake Mead, Cathles⁶ found the observations to be sensitive to the viscosity profile of the entire mantle.

His viscosity-depth results, with depths given below the base of the continental crust, are: 0–75 km, 0.04×10^{22} poise; 75–1,000 km, 1.0×10^{22} poise; and 1,000–2,700 km, 0.8×10^{23} poise, all with an estimated accuracy of 10%. Because of the relative completeness of Cathles's model, I shall use his results to determine whether a model of mantle-wide convection can be constructed. It is also important that the post-glacial rebound rates are comparable to plate tectonic rates, so that the inferred pseudoviscosities may be directly applicable.

Morgan⁷ has suggested that mantle-wide convection is expressed as plumes no more than a few hundred kilometres across. About 20 of these plumes, all under prominent volcanic features, are the only upward convective movement in Morgan's model and everywhere else in the lower mantle the motion is downward. Morgan^{7,8} and Hey⁹ inferred that this plumelike convection is a major drive behind the surface plate motions. The association of 17 of the 20 plumes with spreading ridges and the ability of a mid-ocean plume to continue generating aseismic ridges on two plates hints that there is some causal connexion keeping the plume centred under the locus of divergence of adjacent plates. Circumstantial evidence like this must accumulate in large amounts if it is ever to be convincing by itself. But a quantitative model of the convection would be very helpful in evaluating the plausibility of Morgan's plume hypothesis. An accurate model, with the full physics intact, is not even remotely possible at this time, therefore I have tried to construct the

simplest model that retains plate tectonics as the model's surface expression.

Thermal Balance

The model sought is one of fully-developed, steady-state convection. Although Rice¹⁰ has discussed non-steady convective mechanisms, as yet there is little in the marine magnetic records to require either episodic or time-modulated convection. The simplest hypothesis on heat transfer is that all processes in the lower mantle are adiabatic, with the addition of self-heating due to radioactivity. I will assume that conductive heat transfer is important only in the shallow region where the plates are created and reassimilated. Later in this article, I show that convection, once established, would make radiative heat transfer impossible.

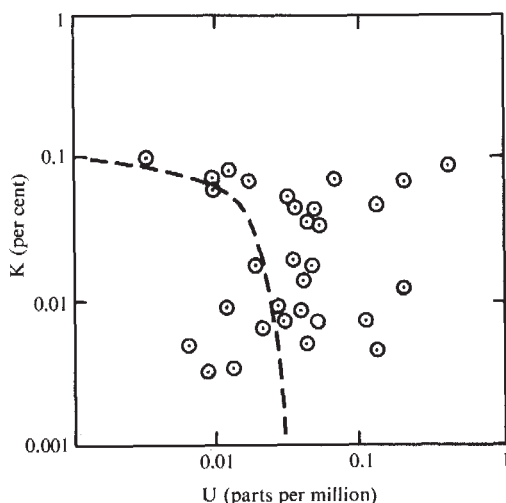


Fig. 1 Potassium and uranium contents of peridotites²⁹⁻³³. The dashed line is the locus of points which would cause the entire mantle to give the oceanic heat flow.

Central to this model will be a balance of the thermal inputs and outputs and a balance of forces between a pressure head and a viscous drag. For the energy balance, the simplest assumption is that the radioactive heat production in the entire mantle equals the oceanic heat flow. Presumably continents contain enough internal radioactivity to supply their own heat flow¹¹. Fig. 1 shows that the uranium and potassium analyses of peridotites, especially lherzolites, are scattered around the line corresponding to the oceanic heat flow, therefore it seems unnecessary to postulate tidal energy, freezing of the inner core, or core radioactivity as additional energy sources. The loss of energy from the system will be entirely accounted for by the growth of oceanic plates. In effect, the material brought up from the plumes spreads radially, and this plume-derived material is the asthenosphere. At the upper surface, seawater sets an isothermal boundary condition and the asthenosphere grows a rigid upper boundary layer.

Although McKenzie¹² uses the cooling of a fixed-thickness lithosphere to account for the heat flow observations, the evidence shown in Fig. 2 suggests that the lithosphere continues to thicken out to the oldest oceanic crust. Therefore, as a first approximation, I prefer to regard plate growth by thermal conduction as the only heat output from the system. The cooled upper boundary layer becomes enormously less viscous than the asthenosphere, and the surface then follows

the Euler theorem of rigid plate tectonics. The asthenosphere beneath the plates still follows the rules of fluid mechanics, so that the asthenosphere motions are not everywhere identical to the plate tectonic motions. But it is my contention that the plates are riding in the general direction, and at the averaged rate, of the asthenosphere flow beneath. I do not, however, wish to imply that the asthenosphere is "driving" the plates because plate growth is the principal heat output from the system and therefore the plates themselves are a vital link in the convective process. The data in Fig. 2 seem not to support the hypothesis that deep material convects up to the base of the plates, gives up some heat by conduction through the plate, and then sinks downward. If the oceanic plates form a thermal boundary layer that grows as the square root of the time, several additional observations seem to fit. The oceanic crust has an increasing tendency to sink as it gets older and there is little hope of finding a scrap of very old ocean floor that has been overlooked by the seafloor spreading process. Phenomena like the double trench in the Marianas and the Ryukus, and the high density oceanic lithosphere of Press¹, are more understandable if very old oceanic crust is gravitationally unstable.

Force Balance

The balance of forces on the mantle-wide convection consists of viscous dissipation balanced against a hydraulic head due both to thermal expansion and to temperature dependent shifts of the mantle phase transitions. The annual volume, q , brought up by the plumes and pushed horizontally through the asthenosphere must equal the downgoing flow that cycles through the lower mantle. First, one wants to know whether the resistance to flow is dominantly in the lower mantle or dominantly in the asthenosphere. Deferring, for the moment, a discussion of the specific flow geometry, the resistance can be approximated by a Poiseuille flow between parallel plates (Table 1). From Table 1

$$q = \frac{t^3 \rho g h}{12 \mu l} = \frac{t^3 \rho g h}{12 \mu l}$$

$$h_{\text{asthenosphere}} = 500 h_{\text{deep}}$$

Because the asthenosphere head losses are roughly 500 times larger than the lower mantle head losses, the model must emphasize the hydraulics of the asthenosphere, with the knowledge that the lower mantle will follow along because of its much smaller resistance to flow. On a smaller planet, this might not be true: on Mars the third power of the phase transition is 15 times larger.

Table 1 Parameters of Poiseuille Flow

	Asthenosphere	Lower mantle
Thickness, t	100 km	2,000 km
Density, ρ	3 g cm ⁻³	5 g cm ⁻³
Gravity, g	10 ³ cm s ⁻²	10 ³ cm s ⁻²
Viscosity, μ	4 × 10 ²⁰ dyne s cm ⁻²	10 ²² dyne s cm ⁻²
Length, l	5,000 km	5,000 km

Rice's suggestion¹⁰ for drawing an equivalent circuit helps to clarify the discussion. Fig. 3 shows that the current is determined by the resistance R_1 and the sum of the voltages $E_1 + E_3$. Previous arguments about the causes of plate motion tended to try to choose between E_1 (upwelling) or E_2 (sinking). The sum of the two potentials in the Earth turns out to be dominated by the temperature difference between upward and downward flow. Because the hydraulic head losses are dominantly in the asthenosphere, the model will focus on the fluid mechanics of the asthenosphere. The vertical heights in the asthenosphere are rather small, com-

pared to the entire mantle. The height over which the head due to the temperature displacement of phase transitions will be equal to the head due to thermal expansion is given by:

$$\rho\alpha\Delta Tgh = \left(\frac{\rho_1 - \rho_2}{\rho_1}\right) \left(\frac{dP}{dT}\right) \Delta T \quad (1)$$

where ΔT is a temperature contrast, α is the thermal expansion at constant pressure, h is the height of the column of material, ρ_1 and ρ_2 are the densities above and below the phase transition, and dP/dT is the slope of the Clapeyron curve for the phase transition. For typical magnitudes, the phase transition is about as effective as the thermal expansion of an 1,800 kilometre high column. For the 100 or 200 km high columns in the asthenosphere I will ignore thermal expansion and treat the fluid heads as entirely the result of the phase transition.

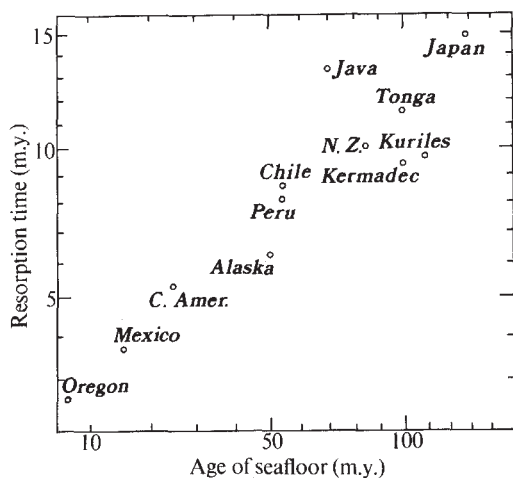


Fig. 2 Older oceanic plates require longer times to be thermally resorbed in the mantle. The resorption time is the distance from the trench to the deepest earthquake, divided by the plate-to-plate closure rate at the trench. Both the growth of oceanic plates and their resorption are diffusive processes that should be governed by the square root of the time. Therefore both axes are plotted on square root scales. Redrawn, with permission, from Morgan (in preparation).

The actual phase transitions between the lower mantle and the asthenosphere are undoubtedly quite complex. For the present model, however, all that is needed is the hydraulic head produced by a temperature difference extending across the entire set of phase transitions, because the hydraulic effect is due to substituting the density above the uppermost phase transition for the density below the lowermost phase transition. For this limited purpose, one can consider the metastable equilibrium between the mineral assemblage in the asthenosphere and the isochemical mineral assemblage in the lower mantle. Here, phase transition will be used in the singular to refer to the total effect of the 350 and 700 km phase transition. As an approximation, I am forced to choose the only lower mantle mineral assemblage for which there are adequate thermodynamic data: forsterite + clinoenstatite $\rightarrow$ 2 stishovite + 3 periclase. It is entirely possible that stishovite and periclase are the dominant mineral phases in the lower mantle, but Ringwood¹³ discusses a number of alternative mineralogies which have not yet been synthesized. For the moment we will hope that the thermodynamic properties of the lower mantle are reasonably close to those of the stishovite-periclase assemblage. The Robie-Waldbaum

tables¹⁴ give an internally consistent set of free energies, entropies, and molar volumes from which the equilibrium curve in Fig. 4 was calculated. The slope of the equilibrium curve, dT/dP , calculated by the Clapeyron equation from the entropies and volumes, is in the direction that causes the phase transition to promote convection¹⁵. In the hot, upwelling plume the transition to the less dense phase happens at a greater pressure and the resulting hydraulic head was given earlier in equation 1.

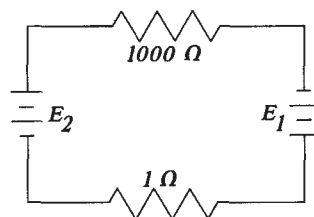


Fig. 3 Equivalent circuit emphasizing the dependence of flow through the asthenosphere on the difference in potential between upcoming and downgoing flows, and the dominance of the upper mantle in the resistance.

An element moving adiabatically through the phase transition must go through a temperature step if the entropy of the products is to equal the entropy of the reactants. At surface pressure the temperature step would be $T\Delta S/c_p$. At high pressure the entropies of the low density phases change more than the high density entropies, therefore it is worthwhile correcting the entropies for compression:

$$\Delta T = \frac{T(\Delta S - \alpha P \Delta V)}{c_p}$$

For the olivine plus pyroxene going to oxides at 180 kbar, using the Robie-Waldbaum data¹⁴, the isentropic temperature step amounts to 120 K. Ringwood¹³ objected to convection through the phase transition because the temperature step could not be maintained by thermal conduction. As long as the plume diameter and the upwelling velocity are large enough to prevent thermal equilibration with the surroundings, the interior of the plume proceeds through the phase transition while creating as little entropy as possible. Later in the same article, Ringwood points out that the downgoing plates plunge through the phase transition region. A straightforward conservation of mass argument would suggest that somewhere else material should be coming up through the phase transition. An equivalent way of viewing the problem is to extend the concept of potential temperature¹⁶ to include the isentropic passage through a phase transition.

Mantle Temperatures

I am now in a position to infer temperatures inside the Earth. As a starting point I choose a Hawaiian lava fountain which spurts 1,400 K lava at velocities exceeding 100 km h⁻¹. Because it seems unlikely that this lava has paused to exchange heat with the crust, I will presume that only adiabatic cooling associated with pressure release has affected the lava. The slope of the adiabat, given by $-\alpha VT/c_p$, is interrupted by a negligibly small step at the depth at which the lava separated from the solid mantle. The step is small, not because the heat of fusion is small, but because only about 3% of liquid is separated isothermally from the solid. The adiabatic extrapolation continues downward to the phase

transition, where there is a net offset of 120 K, and from there down adiabatic behaviour should characterize the interior of the upwelling plume right down to the base of the mantle. The calculated entropy increase associated with

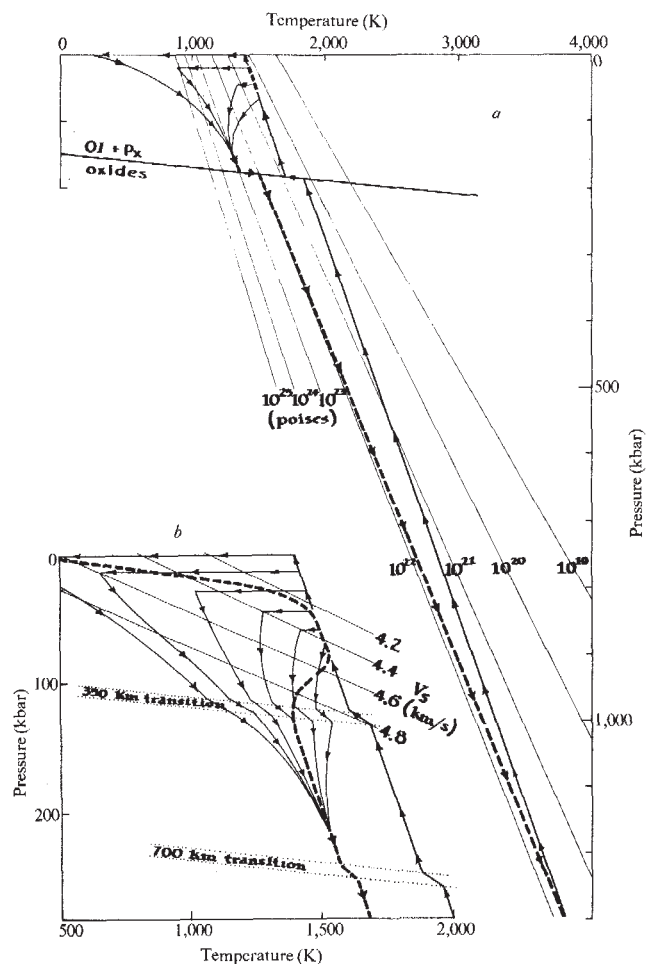


Fig. 4 Flow paths in pressure-temperature space. The upward arrows are drawn at constant entropy, with the surface pegged at the 1,400 K temperature of basaltic lavas. The mean temperature of the downgoing flow is 330 K colder, determined from the requirement that the phase transitions be able to drive the flow through the asthenosphere. The heavy dashed lines indicate the pressure-temperature conditions in the "normal" Earth away from the plumes and trenches. *a*, The entire flow down to the core-mantle boundary. The phase transitions are grouped into a single overall reaction. The lightest lines are viscosities calculated from the Ree-Eyring equation with the activation energy and volume set to 40 kcal mol⁻¹ and 2.62 cm³ mol⁻¹, which causes the heavy dashed lines to match Cathles's viscosity profile⁶. *b*, An enlarged view of the *P*-*T* paths in the upper mantle, with two phase transitions having the widths suggested by Ringwood¹³. The heavy dashed line shows the pressures and temperatures under an oceanic plate that is not yet cold enough to move down a trench. This "normal" oceanic temperature profile is not offset at the 350 km phase transition because penetrative flow may be taking place only at plumes and trenches. The lightweight lines are the shear velocities for "pyroxene pyrolite"¹¹ and the heavy dashed temperature profile traces out shear velocities in good agreement with oceanic shear velocities¹.

viscous dissipation is too small to show on Fig. 4. Therefore in this example the flow process is much closer to a constant entropy flow than to a constant enthalpy process¹⁷. The temperature inferred at the mantle-core boundary is 3,800 K, but the uncertainty in heat capacity and com-

pressibility would easily fit the 4,800 K calculated for the top of the core by Higgins and Kennedy¹⁸.

If the lavas over the plume can be used to infer the temperature structure in the plumes, what about the temperature structure of the downgoing material? The downgoing plate itself is of considerable thermal complexity^{12,16}. But as I mentioned earlier, the parameter we need is the difference in potential between the upwelling and downgoing material. The driving force in the shallow part of the system is the difference in head between the plume and the place where material goes back down through the phase transition. At the depth of the phase transition the plates have been partially or completely warmed up. Of course, the plate is warmed up only at the expense of cooling down an equivalent amount of adjacent material in the asthenosphere. Although we want the average temperature of the downgoing material, there is no obvious way of extracting the temperature from observations. Therefore it is necessary to turn to an indirect method.

The flow in the asthenosphere will be similar to flow between parallel plates at a very low Reynolds number. Because the plumes resemble point sources and the descending plates create line sinks, the system will be modelled as radial flow. The Poiseuille equation transformed into a form for radial flow is:

$$q = \frac{\pi r^3 \rho g h}{6\mu \ln(r_2/r_1)} = \frac{\pi r^3 (\rho_2 - \rho_1) (dP/dT) \Delta T}{6\mu \rho_1 \ln(r_2/r_1)} \quad (2)$$

The viscosity⁶, the densities⁷, and dP/dT (ref. 14) are all available. The thickness, which appears as the third power, is the greatest uncertainty. Clearly where the plate motion is at high angles to the asthenosphere motion, t refers simply to the asthenosphere thickness. But, as mentioned earlier, the plate motion is probably in the averaged direction of the asthenosphere motions. Where these two motions are parallel, the flow is geometrically similar to half of the Poiseuille flow with the seafloor taking the place of the un-sheared midplane between parallel plates. For this condition, the proper thickness in the Poiseuille equation would be twice the depth of the base of the asthenosphere. Observations of the asthenosphere thickness are notoriously variable, and I have taken the expedient of using a round 100 km as the appropriate thickness. The radius of the plume can be estimated either from the size of the associated volcanic field, or by assuming the cross sectional area of the plume equals the peripheral area where the plume intersects the 100 km thick asthenosphere. Using the second method, I estimate a 200 km radius for the plume. The outer radius, where material returns to the lower mantle, is estimated by dividing the Earth's surface into 20 equal areas, each dominated by a single plume, and the radius of each area turns out to be 5,000 km. Substituting these magnitudes into equation 2 gives an expression in q , the total volume of lower mantle brought up each year through the 20 plumes, and ΔT , the temperature difference between material entering and leaving the asthenosphere:

$$\frac{q}{\Delta T} = \frac{20\pi t^3 (dP/dT)}{6\mu \ln(r_2/r_1)} \quad (5)$$

A second relationship between q and ΔT comes from the restriction that, in this model, the radiogenic heat from the mantle can be transferred to the seafloor only through the convective mechanism. Therefore the oceanic heat flow is determined by the product of q and ΔT .

$$q \cdot \Delta T = \frac{\text{ocean area} \times \text{heat flow}}{\rho c_p} \quad (6)$$

Solving equations 5 and 6 simultaneously gives a ΔT of 330 K and a q of $580 \text{ km}^3 \text{ yr}^{-1}$. One can now insert in Fig. 4 the downgoing flow, and its temperature offset at the phase transition, at a mean temperature 330 K lower than the temperatures in the plume. The heavy dashed lines in Fig. 4 emphasize that in the asthenosphere the high-temperature material brought up by the plume is the majority phase and the downgoing plates occupy only a small area behind trenches. Below the asthenosphere the material on the downward leg of the cycle occupies most of the volume and the plumes are in the minority.

Temperature Inversion

A surprising result emerges: beneath most of the Earth's surface (except at trenches and plumes) there is a temperature inversion at the base of the asthenosphere. The inversion exists because the 330 K temperature difference, needed to supply the driving force and heat flow, is larger than the 120 K isentropic offset across the phase transition. A temperature inversion, although not a feature of most Earth models, is consistent with the seismic data. Birch^{19,20} calculated two upper mantle temperature profiles from seismic velocities, and both showed temperature inversions of about 300 K in the depth range from 150 to 250 km. Although Birch discussed the data in terms of selecting other models in order to eliminate the apparent temperature inversion, I prefer to accept the shapes of the Birch temperature profiles at face value as confirmation that a temperature inversion does exist. Beneath the phase transition, the downgoing material is slowly heated by radioactive decay. This self-heating must close the circuit in Fig. 4 by having a superadiabatic gradient of 330 K over 2,000 km, very close to the 0.1 K km^{-1} superadiabatic gradient interpreted from seismic velocities².

The thermal balance and material balance for the upper mantle is readily checked from the known rate of growth of the plates. An area of 2.6 km^2 of oceanic plate is created and destroyed each year²¹. If the plates, just before leaving the surface, reach 100 km in thickness then the annual throughput of the platemaking process is $260 \text{ km}^3 \text{ yr}^{-1}$. The remainder of the $580 \text{ km}^3 \text{ yr}^{-1}$ brought up by the plumes passes through the asthenosphere and is cooled by the downgoing plate. The temperature gradient in the mature plate should run from 276 K at the surface to 1,400 K at the base, or a mean temperature about 560 K cooler than the potential temperature of the material coming up the plume. The heat balance can be illustrated by the rough agreement between the heat brought up the plume ($550 \text{ km}^3 \text{ yr}^{-1} \times 330 \text{ K}$) and the heat lost by the plates ($260 \text{ km}^3 \text{ yr}^{-1} \times 560 \text{ K}$).

The temperature inversion postulated in this model nicely explains a peculiarity in the Cathles⁶ viscosities. Several years ago, when the need was to explain the asthenosphere as a viscosity minimum, Cook²² used the Ree-Eyring equation for an activated process, along with a temperature profile, to explain a viscosity minimum in the upper mantle. The Cathles viscosities contain a maximum in the 75–1,000 km depth range. My initial attempt to fit the Ree-Eyring equation to Cathles's observations using a linear temperature gradient with depth led to a negative volume of activation, which is nonsense. With the temperature inversion of the present model, the Cathles viscosities lead to a positive volume of activation of $2.62 \text{ cm}^3 \text{ mol}^{-1}$ and an energy of activation of 40 kcal mol^{-1} , which is well within the range expected theoretically^{23,23}.

The postulated temperature inversion can be seen in a larger context if one considers the necessary properties of self-heated convection. One cannot infer Bernard-like cells with a circulation around a "dead" centre. With self-heated convection that dead centre would eventually become very hot. But, if the cell can transform the dead centre into a

surface with countercurrent flow on opposite sides of the surface, all elements, except those right in the surface, are moving. The countercurrent surface has a thickness set by the thermal diffusivity; that is, those elements which can conduct heat out of the countercurrent surface are exempt from the requirement that all elements be in motion. My suggested temperature inversion beneath the asthenosphere and the walls of Morgan's plumes^{7,8} should be continuous with one another and together they are interpreted to be a countercurrent surface. Fig. 5 is a diagram of the suggested countercurrent flow, but it is not yet certain whether the temperature inversion, and the countercurrent flow, is associated with the 350 km phase transition, or whether it is shallower. Although the downgoing material, comprising most of the lower mantle, is moving with velocities of only about 1 mm yr^{-1} , the thermal diffusivity would have to be very high to carry heat up the down staircase. A rough estimate of the required thermal diffusivity is obtained by factoring the diffusivity into a velocity times a distance:

$$D = \frac{\sigma}{t} \cdot \sigma = (3 \times 10^9 \text{ cm s}^{-1}) \cdot (2 \times 10^8 \text{ cm}) = 0.6 \text{ cm}^2 \text{ s}^{-1}$$

This required diffusivity is much larger than recent estimates, including radiation, of the thermal diffusivity in the lower mantle²⁴.

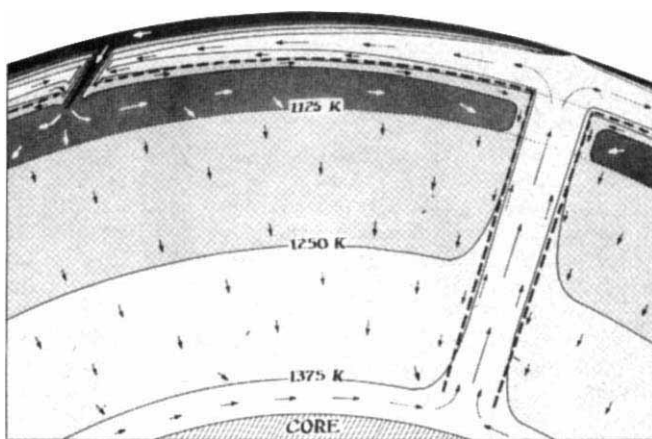


Fig. 5 Potential temperature distribution in the Earth. The potential temperature is the temperature that a segment would have if brought to the surface, and through the phase transitions, at constant entropy. The countercurrent surface separating upcoming and downgoing flows is shown as a heavy dashed line and the phase transitions are shown as dotted lines. Although the details are not certain, this diagram is drawn with the countercurrent surface following the 350 km phase transition. The isotherms are drawn to give a temperature gradient, and therefore a potential gradient, on the 350 km transition to drive material away from the root of the trench. The illusion that the trench is smaller than the plume exists because the trench has a long extension perpendicular to the cross section whereas the plume is cylindrical.

The residence time for material in the lower mantle is obtained by dividing the $900 \times 10^9 \text{ km}^3$ lower mantle volume by the $580 \text{ km}^3 \text{ yr}^{-1}$ brought up by the plumes, giving $1.5 \times 10^9 \text{ yr}$. This particular residence time explains a well-documented peculiarity of the lead isotopes from oceanic islands. The recent partial melting event that produced the lavas was preceded by an earlier fractionating event 1.5 to $2.0 \times 10^9 \text{ yr}$ earlier^{25,26}. It is very difficult to generate a mantle-wide event to fractionate isotopes at a single definite time. In the present model the earlier isotopic fractionation occurred, not

in the bulk mantle, but near the surface on the previous trip through the asthenosphere. If so, the lead isotope observations give a very definite measure of the residence time.

If the asthenosphere is driven by temperature differences at phase transitions, there should be variations in the depths to the phase transitions. The temperature contrast of 330 K leads to a relief on the phase transitions of about 30 km. With compressional wave velocities of 8.5 km s^{-1} above and 11.5 km s^{-1} below the phase transitions, teleseismic compressional wave anomalies of about 1 s are to be expected. Although anomalies of about this magnitude exist (early arrivals near trenches and late arrivals above plumes), the seismic delays cannot uniquely be attributed to relief on the phase transitions. Higbe and Stacey²⁷ have shown that the satellite geoid anomalies are best explained by relief on the phase transitions. The prediction of surface topography and of gravity is the least quantitative aspect of my model. The model does predict regional topographic highs at the plume sites because of the high hydrostatic potential in the asthenosphere. There is a regional slope towards the sinks at the trenches, but the slope of the seafloor (about 4 km) is about half as large as the potential difference given by substituting 330 K in equation 5. Unfortunately the topography, and gravity, are the composite effects of several causes. Besides hydraulic head differences in the asthenosphere, there is cooling and shrinking of the plates, and the possibility of the cooler material below the trench spreading out laterally before going down through the phase transitions. Gravity interpretations are less simple because flow in the asthenosphere removes the condition that equal pressure surfaces and equal density surfaces must be horizontal. One of the puzzles of the gravity interpretation is that both upwellings (plumes) and downwellings (trenches) lead to gravity highs⁸. This can be rationalized in a density-stratified Earth because plumes and trenches are both places where material is injected into a layer. The shear stresses associated with radial spreading in that layer support a regional gravity high.

In this model, it is not necessary to postulate a partially molten asthenosphere to explain either the low viscosity or the low-velocity attributes of the asthenosphere. On Fig. 4a contours of viscosity based on a 40 kcal mol^{-1} activation energy and a $2.62 \text{ cm}^3 \text{ mol}^{-1}$ activation volume explain the Cathles viscosity profile. Similarly, shear velocities using the initial shear wave velocity (4.7 km s^{-1}) and the temperature and pressure derivatives from Birch¹⁹ are contoured in Fig. 4b. The suggested temperature inversion gives the shear velocity distribution of Press¹. P wave velocities add no further constraints. Therefore the only remaining grounds for postulating a partially molten mantle would be seismic attenuation. At least the topmost asthenosphere, at the plume sites, must reach the solidus because the areas above are very active volcanically. But there is no requirement in the present model for the bulk of the asthenosphere to exist in a partially molten state.

It is possible that a component of the asthenosphere flow rate can be measured from oceanic bathymetry. Vogt²⁸ has shown that the topographic steps on the North Atlantic section of the Mid-Atlantic Ridge tend to form gigantic wedges with their vertices to the south, away from the suspected plume under Iceland. Vogt interprets the topography as a result of additional basalt added when a segment in the asthenosphere that was either hotter or that contained more fusible elements passed under the spreading ridge. Then Vogt shows that radial asthenosphere flow away from the Icelandic plume, whose velocity falls off as the reciprocal of the distance from the plume, combined with the constant spreading rate on the ridge, would generate a series of topographic wedges whose angles are most acute nearest the plume. If Vogt's method turns out to be applicable on other ridges, it would give the component of the asthenosphere velocity in a direction parallel to the ridge.

Although the present model was constructed with the phase transitions lumped into a single transition, it is possible to redistribute the effects into two phase transitions and I have attempted in Fig. 4b to sketch the actual paths in P, T space. The parallels to the geophysics of the atmosphere and oceans are quite striking. The mantle, ocean, and atmosphere all contain long vertical columns that are near adiabatic equilibrium. If one accepts my Earth model, all three geophysical fluids have temperature inversions. The stratosphere is the atmosphere's dominant temperature inversion. In this view, the main thermocline in the ocean is a major temperature inversion, and a large part of the ocean is a smeared-out extension of that inversion. And the modes of vertical transport are similar: upward transport in the atmosphere is dominated by narrow features such as the giant cumulus columns in the intertropical convergence zone. In the oceans the main thermocline is intermittently open to vertical transport in the Norwegian and Weddell Seas where narrow plumes of material offset a general motion everywhere else in the opposite direction. Morgan's plumes play the same role in the solid Earth, dividing the transport one way into narrow channels and using the rest of the area for the return flow. If Vogt's hypothesis²⁸ is correct, asthenosphere, ocean, and atmosphere might all contain fronts.

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LETTERS TO NATURE

PHYSICAL SCIENCES

Normal Incidence Radiation Trends on Mauna Loa, Hawaii

MONITORING of solar radiation at the Mauna Loa Observatory is part of a benchmark programme which was initiated at the beginning of the International Geophysical Year on January 1, 1958. The geographic and topographic location of the Observatory greatly enhances the quality of the measurements. At an elevation of 3.4 km, the optical path is reduced to about two-thirds of its magnitude at sea level, and at a latitude of 19.32° N, the Sun at solar noon is almost vertically overhead with a zenith angle of less than 4° on 125 consecutive days annually. Hawaii's location, generally upwind of the other islands of the Hawaiian chain and about 3,700 km from the nearest continent, assures that only longlived substances from any but local sources can affect the solar radiation monitored on Mauna Loa. Perturbations of atmospheric opacities from local sources are minimized by a 30 km distance from only sparsely populated civilization centres and the absence of heavy industries anywhere on the island. Frequent orographic rainfalls (about 400 cm annually) to the windward and over existing pollution sources provide a natural cleansing mechanism. The marine trade inversion is usually found below the elevation of the Observatory and traps most of the particulate matter emitted into the atmosphere from local terrestrial sources. Finally, during several hours after sunrise, the monitoring site is exposed to dry, clean descending air from higher elevations in the course of a thermally induced diurnal mountain circulation.

Eight pyrhelimeters have been used in the current programme at one time or another. A continuing problem in comparison between sensors has been uncertainties in calibration constants and stability of the instruments. Initially, all sensors were calibrated in the laboratories of either the manufacturers or the US Weather Bureau. Some were directly compared at the Observatory. Nevertheless, from the descriptive record log maintained by the observers it soon became apparent that there were some differences in the base level of the calibration of different sensors. The largest such difference was nearly 6%, making the data irrational in light of a presently accepted absolute accuracy of 1% in solar radiation measurements. More important, no trends in the amount of solar radiation received at the ground can possibly be established with such a low degree of reliability. Unfortunately, these erroneous data have been published in the *Climatological*

Data, National Summary which is issued monthly by the National Oceanic and Atmospheric Administration. Peterson and Bryson¹ used these published data to determine Linke's turbidity factor and concluded that there has been a steady increase in turbidity at Mauna Loa since 1958. Because of the detrimental consequences such an event could have on the Earth's climate, the original chart record was re-examined and the data were freed from the sensor calibration values by forming the ratio of irradiances through adjacent air masses on days with maximum optical homogeneity². The results did not establish any persistent trend in atmospheric turbidity but documented the short term effects of volcanic activities on the irradiance measured at normal incidence on Mauna Loa.

Fig. 1 shows the transmission factors (in units of the average daily ratio of transmission through adjacent air masses) as function of time for the period 1958–1971. Within a margin of about $\pm 1\%$ fluctuation in data no systematic trend on Mauna Loa can be detected in solar insolation for the period 1958–1962. The decrease in insolation in the summer of 1963 coincides with the eruption of Mount Agung, Bali, during which dust was emitted into the stratosphere^{3–5}. A delayed removal time of the volcanic aerosols in the stratosphere of up to 7 yr is indicated by the data. This may have been caused by the input of additional particles and sulphurous gases by subsequent volcanic eruptions. The sinusoidal curves superimposed onto the data points result from least squares approximations. The upper curve was fitted to the data over the period January 1958 to February 1963, then extrapolated from that time to the middle of 1971. The lower curve is fitted to the data over the period April 1963 to the end of record. It follows that the transmission of solar radiation received by the Earth apparently undergoes annual cycles such that atmospheric transmission is lower during the summer months. On the basis of the data collected before 1963, it follows that the amplitude of the seasonal variations is constant, and also larger than it was after the Mount Agung eruption in 1963. Since about 1969, however, the transmission curve based on the post-Agung data approaches the 1958–62 transmission curve in annual mean, amplitude and phase. Table 1 shows the quantitative relationships between the two time periods given in column 1. Column 2 gives the corresponding transmission equations, where T is the apparent transmission and t is the time in days with $t=1$ on January 1, 1958. The resulting amplitudes in column 3 reveal a 16% reduction owing to volcanic activities in the post-Agung period. This change is statistically significant, based on an F -test with a 95% confidence level. On the other hand, the change in phase angle, represented in column 4 by the annual transmission maximum, appears to be statistically insignificant.

Table 1 Annual Average, Amplitude and Phase of Periodic Transmission Functions for the Pre and Post-Agung Periods

Period	Transmission equation	Amplitude	Annual transmission maximum	No. of observations
1958–1963 (pre-Agung)	$T = 0.9338 - 0.00252 \sin\left(\frac{2\pi t}{365}\right) + 0.00283 \cos\left(\frac{2\pi t}{365}\right)$	0.00379	November 18	175
1963–1971 (post-Agung)	$T = 0.9275 + 0.000005175 + -0.00272 \sin\left(\frac{2\pi t}{365}\right) + 0.00164 \cos\left(\frac{2\pi t}{365}\right)$	0.00318	November 1	318

T = Apparent transmission. t = Time in days with $t=1$ on January 1, 1958.

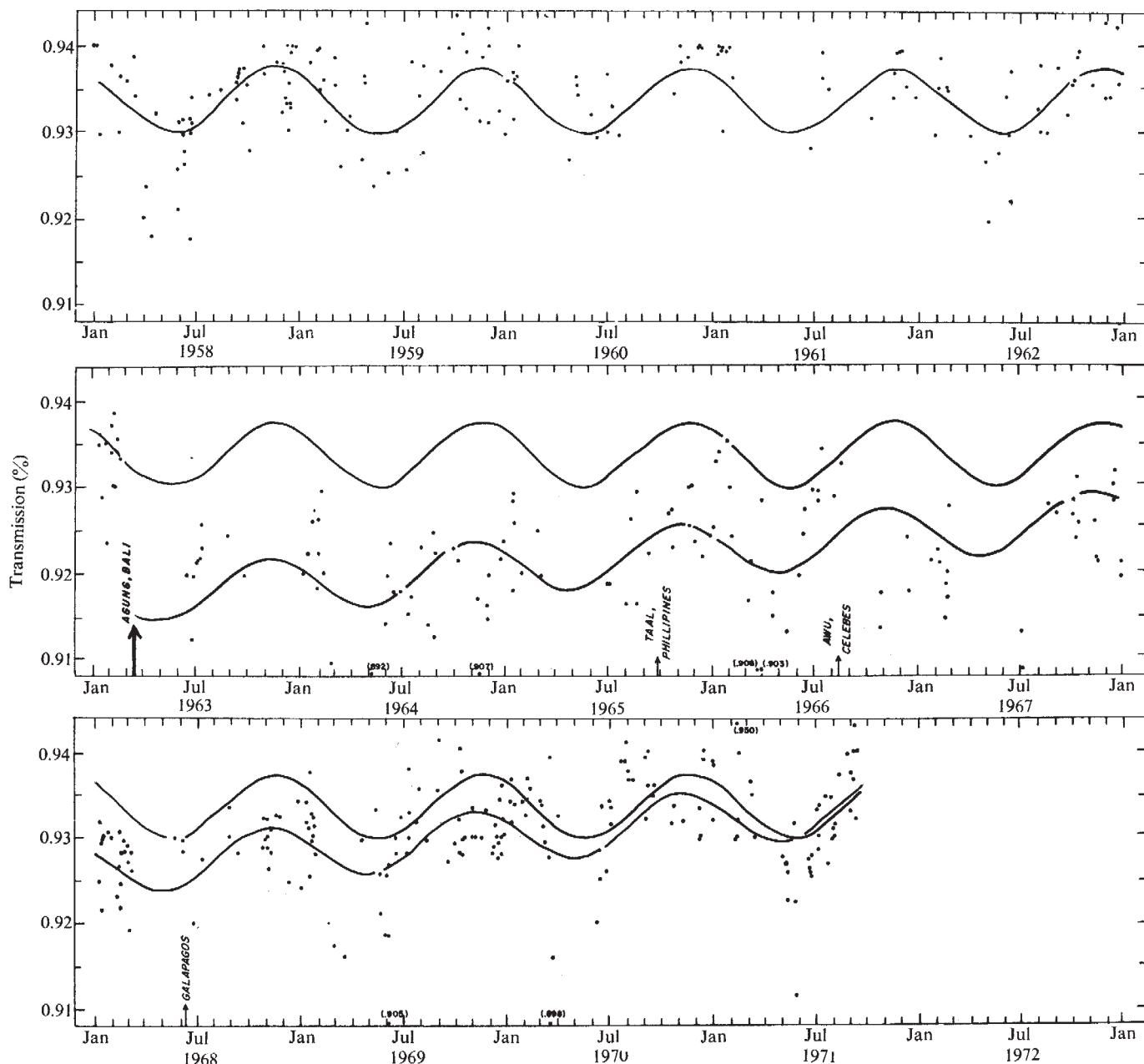


Fig. 1 Transmission factors and least squares approximations for the periods January 1958 to February 1963 (pre-Agung, upper curve), and April 1963 to December 1971. The upper curve was extrapolated to the middle of 1971.

We note, however, that the long averaging time of 8 yr obscures larger variations which are indicated if the data are evaluated on a year to year basis.

The annual turbidity variation is a worldwide phenomenon that has been observed at a great number of remote locations⁶⁻⁸. While it is premature to draw any firm conclusions as to the cause of the seasonal turbidity variations, a few thoughts nevertheless may be mentioned. First, the higher turbidities in summers match the concept of longer aerosol residence times resulting from atmospheric mixing extending to a greater depth due to more intense surface heating. Second, the lower atmospheric transmissions during the summer months could be the result of increased worldwide photochemical aerosol formation caused by the oxidation of volatile organic materials of plant origin in the atmosphere. Third, an increased atmospheric water content during the summer months could yield higher turbidity values.

Whatever its cause, we propose that these turbidity fluctuations take place in the troposphere. This follows from the time scales of recovery of the order of one half year in view of

established stratospheric residence times exceeding one year. It is further substantiated by a reduced amplitude after the eruption of Mount Agung (1963) in spite of a documented heavier particulate load, then, of the stratosphere. Further, the perturbations experienced from 1963 to 1969 suggest that the high amplitudes prior to 1963 and again since 1969–1970 are characteristic of the background aerosol.

Although changes in the average atmospheric transmission level only have been used as criteria for alterations in the background aerosol in the past, the Mauna Loa data strongly suggest that amplitude and probably phase of annual fluctuation in atmospheric transmission are additional parameters which describe the effect of the atmospheric background aerosol on solar radiation. The perturbations imposed on the background aerosol by volcanic activities are clearly documented by the results in Fig. 1 and Table 1. Although we do not know exactly how man-made pollution will affect the annual transmission cycle measured on Mauna Loa, both a reduced amplitude and, possibly, a change of the phase of the turbidity variations as well as a lower annual average of atmospheric

transmission could be indicative of an increased influence of anthropogenic contaminants on the Earth's radiation budget.

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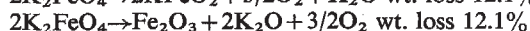
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Anionic Species of Fe in Interstellar Dust

A CRYSTAL-FIELD assignment for the 17,500 cm⁻¹ (5700 Å) and 19,700 cm⁻¹ (5100 Å) bands in absorption spectra of Type I supernovae would support the contention that 6 of the 8 prominent supernova bands (and their diffuse interstellar¹ wavelength-equivalents) have been "parcelled" and assigned correctly to d-d transitions in tetrahedral-Fe³⁺ and octahedral-Fe³⁺. It had been assumed earlier that octahedral- and tetrahedral Fe³⁺ ions are incorporated in the same oxide² (γ-Fe₂O₃) or silicate³ (schorlomite) lattice. Here, I point out that interstellar dust may contain anionic species of Fe, namely FeO₄²⁻ and FeO₂⁻, which are thermally degradable to a likely interstellar material α-Fe₂O₃. (Absorption bands are designated according to their wavelengths in the May 4 spectrum⁴ of SN-NGC-4496.)

The solution spectrum⁵ of FeO₄²⁻ shows two overlapping bands centred at 17,800 cm⁻¹ and 19,700 cm⁻¹, in striking coincidence with the 17,500 cm⁻¹ and 17,700 cm⁻¹ supernova bands. The FeO₄²⁻ ion is purple in solution and in the solid state, so the spectra are expected to be similar. Oscillator strengths for the FeO₄²⁻ transitions (~10⁻²) are considerably greater than for the ⁶A₁→⁴A₁+E(G) transitions responsible for the 4400 Å Fe³⁺ bands^{2,3} in schorlomite (f~3×10⁻⁵) and haematite (~10⁻³). The 800–1,000 cm⁻¹ half-widths of the two supernova bands, when compared to the ~5,000 cm⁻¹ half-width of the FeO₄²⁻ envelope, suggest low dust temperatures, probably <77 K.

Thermogravimetric analysis⁶ has shown that K₂FeO₄ is degraded at 500–600 K in air according to two possible reactions.



No further loss in weight is observed up to 1,100 K. Differential thermal analysis has shown that α-Fe₂O₃ is formed at ~800 K, and accordingly KFeO₂ was postulated as an intermediate in the degradation of FeO₄²⁻ to α-Fe₂O₃. An intermediate compound was isolated but not thoroughly characterized. KFeO₂ has a cristobalite structure⁷ in which all Fe³⁺ ions are tetrahedrally coordinated. Octahedral-Fe³⁺ bands at 6180 Å and 4430 Å are the strongest diffuse interstellar

bands, whereas in supernovae spectra^{4,8} the 5100 Å bands are often at least as intense. It seems that the grains responsible for supernova absorption, in contrast to the diffuse interstellar grains, have not been heated sufficiently in a reducing atmosphere to convert FeO₄²⁻ to α-Fe₂O₃.

The laboratory preparation⁹ of ferrate(VI) requires highly-oxidizing conditions, for example, in Fe/KNO₃ melts or by the action of Cl₂ on alkaline suspensions of Fe₂O₃.nH₂O, conditions that preclude its formation in interstellar space dominated by hydrogen. Ferrate could condense during the expansion phase following supernova explosion; alternatively ferrate could form in the atmospheres of oxygen-rich stars and then be ejected into space. Significantly, Type I supernovae are associated¹⁰ with old stars, probably deficient in hydrogen. Local oxidizing conditions are indicated by the presence of Fe³⁺ ions in dust.

The duration of the rise¹¹ in brightness is ~100 day and the absorption bands appear usually a few days after maximum. The narrowness of the bands and indicated low temperatures of the Fe-bearing dust are inconsistent with condensation from hot supernova shells. Calculations¹² show that 100 day is too short a time for condensed grains to cool to ~77 K. The temperatures of circumstellar grains are determined¹³ by the balance between the rate of absorption of energy at optical and that re-radiated at infrared wavelengths. It is possible that cold, mantled grains existed before the supernova and that the increase in grain temperatures arising from the absorption of light is sufficient to evaporate mantles of, for example, solid H₂. Racah B-parameters¹⁴ suggest increasing temperatures for supernova dust. The maximum distance of the circumstellar grains from the star is 100 light day, at which distances from old cool stars grain temperatures may be close to 3 K.

FeO₄²⁻ gives a better wavelength fit¹⁴ than Mn³⁺ to the 5100 Å and 5700 Å supernova bands. Both ions indicate, from the narrowness of supernova bands, low dust temperatures. The strong points of the present hypothesis are that all supernova bands can be assigned to Fe and that at least two absorbing species are thermally related.

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Microearthquake Survey of the Mid-Atlantic Ridge

THE association of earthquakes with the axis of the Mid-Atlantic ridge is well known¹⁻⁴, and it has been realized that where a median valley existed, the pattern of epicentres straddled it^{5,6}. The first motions and distribution of earthquakes along

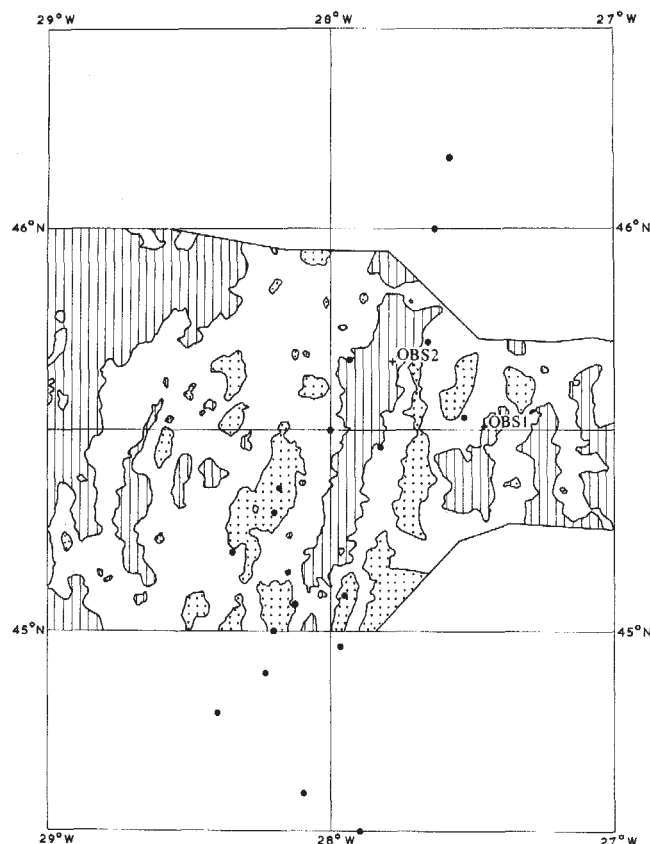


Fig. 1 Bathymetric map of the Mid Atlantic ridge showing positions of seismographs. Bathymetry after Bhattacharyya and Ross (1972) (ref. 16). Water depths greater than 2,600 m hatched, less than 1,800 m stippled. Solid circles mark earthquake epicentres reported for 1963-1969.

fracture zones confirm the hypothesis of transform faults and hence give support to ideas of sea floor spreading and plate tectonics^{7,8}. Seismological observations on Iceland have demonstrated the anomalous nature of the upper mantle beneath the ridge axis⁹⁻¹², but the anomalous character of Iceland itself limits the value of this work. Further progress in the seismological study of the ridge axis requires a greater precision of observation than the present network of seismographic stations can provide. Epicentral location on the Mid-Atlantic ridge is still too crude to allow precise correlations with physiographic features, and depth determination has not progressed beyond a qualitative "shallow". Only by direct seismographic observations on the ridge axis can we resolve these problems and understand more about the tectonic and magmatic processes taking place in the zone where new oceanic lithosphere is being created. Ocean bottom seismographs have therefore been under development over the past few years under the joint sponsorships of the Institute of Geological Sciences and the United Kingdom Atomic Energy Authority.

We report here preliminary results from two seismograph drops onto the Mid-Atlantic ridge carried out in May and June of this year from RRS Shackleton. The first seismograph was dropped into a small sedimented valley some 30 km east of the median valley, the second into the median valley itself.

The geographical coordinates, water depths and operating times of the two instruments are given in Table 1. This particular part of the Mid-Atlantic ridge was chosen because it has been studied in detail¹³⁻¹⁶; it is a "typical area" of ridge, undissected by any significant fractures¹³. The positions of the seismographs in relation to the bathymetry of the area are shown in Fig. 1. Earthquake epicentres reported for the area by the USCGS for the period 1963-69, recomputed where available by the ISC, are plotted on the same map.

The seismographs themselves will be described fully elsewhere. Briefly, each seismograph contains a 3-component short period seismometer (natural frequency 2 Hz) and an external hydrophone. Signals from these transducers and an accurate crystal-controlled clock are recorded in FM form on magnetic tape. An acoustic pinger allows the instrument to be tracked when submerged. In operation the instrument falls freely to the seabed. There it can be tracked acoustically while the ship makes a number of passes overhead. While doing so the ship maintains an accurate radar plot relative to a moored dan buoy and observes a number of satellite fixes. The combination of these techniques allows the geographical position of the seismograph to be determined, under favourable conditions, to an accuracy of 0.1 nautical miles. After a preset time interval the pinger is switched off, the seismometer gimbal is clamped and recording starts. At the end of the recording period the pinger is again switched on, an explosive bolt is fired, the buoyant seismograph assembly releases itself from its sinker and floats to the surface for recovery.

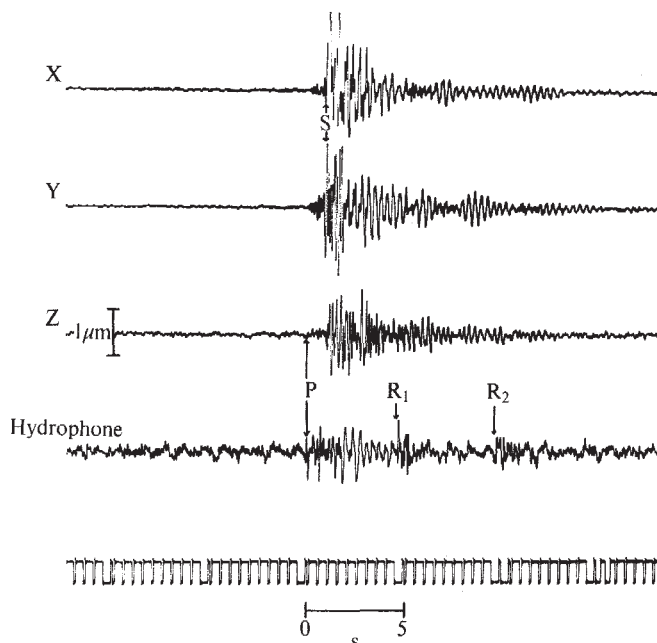


Fig. 2 Earthquake recorded by OBS2. Equivalent ground displacement on the vertical component trace is given for the peak magnification at 6 Hz. Magnification on the horizontal component traces is about half that on the vertical. Orientation of the horizontal components is unknown.

Although the noise levels were similar, radical differences were observed in the seismicities of the two sites. Thirty events per day were recorded by OBS2 in the median valley, but only six per day by OBS1 30 km off the axis. Clear P and S phases

Table 1 Parameters of Ocean Bottom Seismograph Stations

Instrument	Latitude	Longitude	Water depth	Recording ON	Recording OFF
OBS1	45° 30.4' N	27° 27.4' W	2,772 m	1900 Z, May 29, 1972	1500 Z, June 2, 1972
OBS2	45° 40.3' N	27° 47.4' W	3,592 m	2300 Z, June 2, 1972	1900 Z, June 6, 1972

can be distinguished for the larger events, and the S-P times form a consistent pattern. In the median valley S-P times were short, generally about 1 s. Outside the median valley larger S-P times were observed, ranging up to about 7 s. Assuming an S-P velocity of 7 km s^{-1} , this shows that whilst earthquakes recorded in the median valley also originated there (defining the median valley as anywhere between the mountain peaks on either side), those recorded off the axis may also have originated in the median valley. This and the much higher seismicity of the OBS2 site point to the same general conclusion—that the microearthquake activity is largely confined to the median valley. The fact that only short S-P times were recorded by OBS2 may further indicate that propagation in the median valley itself is poor.

Fig. 2 shows a record obtained by OBS2 in the median valley. Clear P and S phases can be observed giving an S-P time of 1.0 s. In addition to a particularly clear P arrival, phases which have been singly and doubly reflected at the sea surface can be distinguished on the hydrophone trace. Fig. 3 shows a record obtained by OBS1. The S-P time in this case is 4.5 s. The S phase, best identified on the horizontal components, is just preceded by the arrival of the sea surface reflexion on the hydrophone trace.

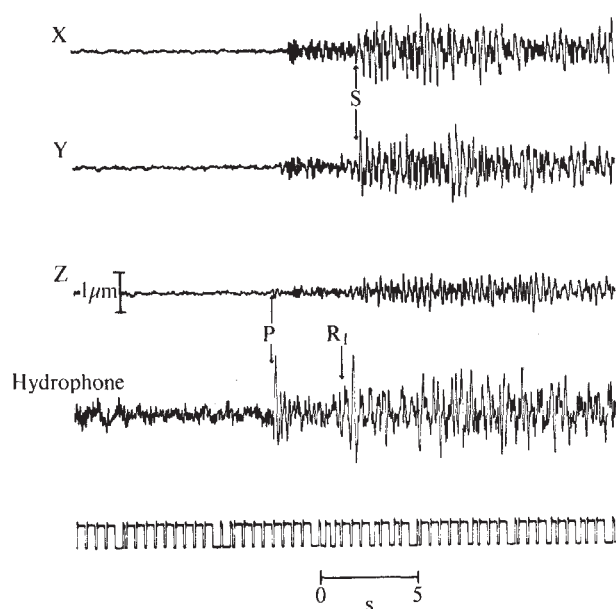


Fig. 3 Earthquake recorded by OBS1. Equivalent ground displacement on the vertical component trace is given for the peak magnification at 6 Hz. Magnification on the horizontal component traces is about half that on the vertical. Orientation of the horizontal components is unknown.

The records also demonstrate the relative value of the transducers employed. Most of the seismic energy is carried in the S-waves, especially at close range, and these are best detected by the horizontal components of the seismometer. Thus the smallest events are only detectable on the horizontal components. The P wave gives a more impulsive beginning on the hydrophone than on the vertical component of the seismometer, but this may be partly a characteristic of our instruments. It is interesting to note that had OBS1 and 2 operated simultaneously, very few events would have been recorded by both instruments. This means that future operations with an array of seismographs will require that they be placed not more than about 10 km apart and probably all in the median valley itself.

No teleseismic events were detected by either seismograph although, according to the LASA and NORSAR bulletins, a number of events with $m_b > 5.0$ occurred at suitable range during the recording period. More detailed processing may still

extract a teleseismic arrival, but the combination of low Q beneath the ridge axis and relatively high noise levels at the recording sites makes this unlikely.

The records are now being studied in detail and the results of this study will be published elsewhere.

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Seismic Wave Scattering near the Core-Mantle Boundary: a New Interpretation of Precursors to PKP

THE so-called precursors to PKP consist of a train of arrivals preceding the core phase PKIKP, of small but variable amplitude, and commonly observed in the distance range 125° to 143° . Interpretations of this phenomenon have included dispersion near the boundary of the inner core^{1,2}, diffraction from the PKP caustic³, sharp upward refraction within one or more transition layers surrounding the inner core⁴⁻⁶ and reflexions from small discontinuities at the boundaries of such transition layers^{7,8}. In order to take account of certain unexplained features of the observations, Haddon⁹ recently advanced the alternative hypothesis that precursors are the result of scattering of PKP waves from irregularities in the vicinity of the core-mantle boundary. We examine the scattering hypothesis in more detail, and present evidence in its favour.

The P velocity distribution in the Earth is such that PKP waves originating at a surface focus form a caustic surface which intersects the core-mantle boundary and the Earth's surface at angular distances of 117.5° and 143° respectively (Fig. 1). (Times and distances given here are based on the Jeffreys-Bullen tables.) The presence of irregularities in the vicinity of the core-mantle boundary would result in scattered waves in addition to the direct core waves. The earliest arrivals at the surface would be waves scattered both on entry to and exit from the core. To the extent that amplitudes of scattered waves depend on the direct wave amplitude at the point of scattering, however, waves scattered from the caustic would have much larger amplitudes (and are thus more likely to be detected) than waves first divergently scattered before entry

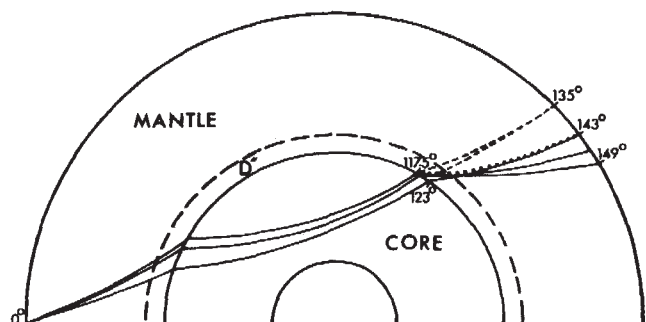


Fig. 1 The PKP caustic (---) within the mantle, shown in relation to associated PKP ray paths. Also shown are ray paths (---) corresponding to waves scattered from the core-mantle boundary and from within the D'' layer to an epicentral distance of 135°.

into the core and scattered again after re-entering the mantle. We therefore restrict our discussion to waves scattered from the caustic surface within the transition layer D'' in the deepest 200 km of the mantle¹¹, with ray paths of the kind shown in Fig. 1.

PKP waves travelling through the core first impinge on the core-mantle boundary at the intercept of the boundary with the caustic surface. Waves scattered from this intercept would be the earliest singly scattered arrivals at the surface. The "minimum time" curve thus defined has an absolute minimum at an epicentral distance of 117.5°, corresponding to scattering from the intercept in a radial direction through the mantle.

In Fig. 2 we show the minimum time curve and a curve corresponding to scattering from the caustic at a point 200 km above the core-mantle boundary in conjunction with the Jeffreys-Bullen curves for PKP. Also shown are precursor data tabulated by Hai², Bolt⁴, Adams and Randall⁵ and Engdahl¹², corrected to surface focus where necessary. The earliest observations fall on or near the minimum time curve, and most of the observations are distributed fairly uniformly between the two curves. Although the first arrival times are well defined, fluctuations in observed onset times are to be expected because of variations in signal amplitude and differences in signal-to-noise ratio on individual records. A concave upward curvature in the trend of the data is also apparent in the figure, matching the characteristic curvature of the scattered wave curves.

Table 1 Events from ISC Bulletins used in Fig. 3

Year	ISC vol. No.	ISC event No.
1964	6	229, 341, 371
	7	681, 696, 701
	9	243
	10	299
	11	304
	12	33, 493
1965	5	520, 755
	6	619

These features can be seen also in plots of precursor data by Buchbinder⁸ and others¹³⁻¹⁵ and in collations of ISS bulletin data by various authors¹⁶⁻¹⁸. As a further example, Fig. 3 shows arrivals reported as PKIKP for 14 events in ISC bulletins for 1964-1965 (Table 1). Also shown in Fig. 3 is an extension of the PdP curve of Bolt *et al.*¹⁸, which may account for some of the observations between 115° and 120°.

In connexion with previous interpretations which require reflexions or refractions from transition layers surrounding the inner core⁴⁻⁸, we note that the variations in times and amplitudes of the observed "phases", and the concave upward curvature of the precursor observations, are very difficult to

account for in terms of reflected or refracted branches, which would be necessarily discrete and virtually straight throughout the range of observations; whereas such features are a natural consequence of the scattering hypothesis. Also, the coincidence of a transition boundary occurring at just the right depth to produce arrivals which fall so close to the minimum time curve for scattered waves would be remarkable.

Finally, we present evidence from two array studies of travel time gradient ($dT/d\Delta$) which strongly supports the present interpretation. The first is an observation by Qamar¹⁹ of a precursor signal from a Java earthquake recorded at the LASA array at a distance of 127.2°. As shown in Fig. 2, the time and $dT/d\Delta$ of this signal correspond closely to those predicted by the minimum time curve. Qamar himself notes that the $dT/d\Delta$ (1.9-2.2 s deg⁻¹) is in disagreement with a value of 2.8 s deg⁻¹ given by the Bolt model, and is contrary to a straight line interpretation of precursor times for this earthquake, which would require a $dT/d\Delta$ of about 3.1 s deg⁻¹. The second concerns an "unidentified signal" reported by Wright and Muirhead²⁰ from an analysis of signals recorded at the Warramunga seismic array in Australia from a nuclear explosion in Novaya Zemlya at a distance of 106°. The signal arrived from the reverse azimuth with a travel time of 19 min, 21.5 s, and a $dT/d\Delta$ (corrected for local structure) of 2.78 s deg⁻¹. In striking agreement with this, waves scattered from the caustic at a point 140 km above the core-mantle boundary would arrive from the reverse azimuth with a time of about 19 min 21.5 s and a $dT/d\Delta$ of about 2.7 s deg⁻¹.

A scattering layer near the core-mantle boundary would produce scattered waves associated with other core phases. A unique feature of scattering from a caustic, however, is that the scattered wave appears as a first arrival in the shadow zone in front of the caustic. In contrast, waves scattered to distances at which the associated direct wave follows a minimum time path must arrive later than the direct wave, and will simply contribute to the coda of the recorded phase. Precursors to

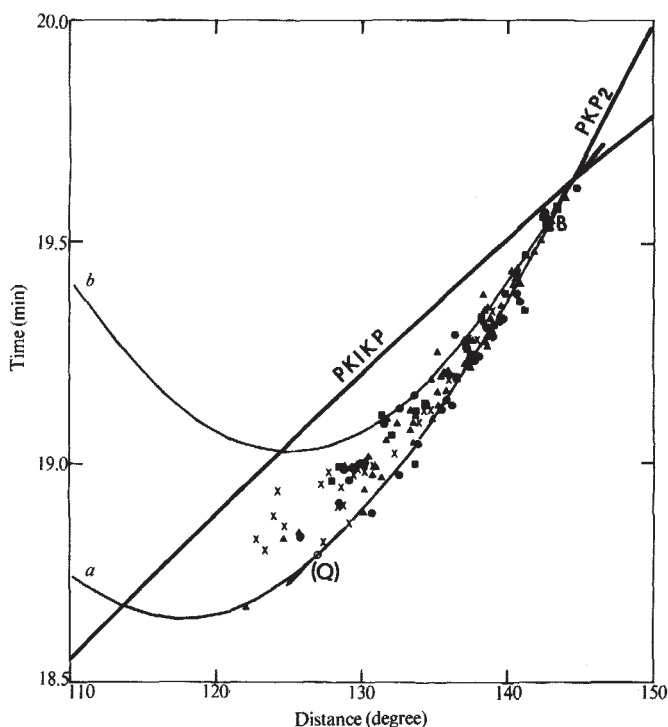


Fig. 2 Published precursor data compared with time/distance curves given by the scattering hypothesis. Curve (a) is the minimum time curve; curve (b) corresponds to scattering from a level 200 km above the core-mantle boundary. The heavy lines are the Jeffreys-Bullen PKP curves, with the surface caustic at point B. Data sources: x, Bolt⁴; ●, Adams and Randall⁵; ■, Hai²; ▲, Engdahl¹². (Q) is an observation of time and $dT/d\Delta$ of a precursor signal at LASA by Qamar¹⁹.

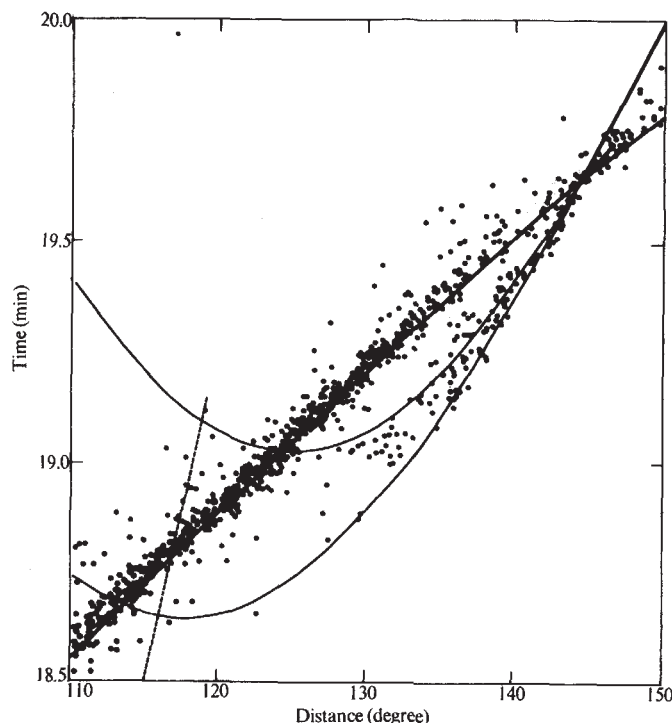


Fig. 3 Data listed as PKIKP residuals in ISC bulletins (Table 1). The solid curves are the same as in Fig. 1. The dashed line is an extension of the PdP curve of Bolt *et al.*¹⁶.

PKKP are to be expected on the present interpretation, but may be difficult to detect in the codas of preceding signals.

In conclusion, we note that the inferred existence of transition layers in the outer core is presently based entirely on the evidence of precursors to PKP. The re-interpretation of precursors presented here removes the need to postulate structural complexities in this region.

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Jurassic Palaeomagnetism

WE have presented some tentative palaeomagnetic results from a Jurassic sedimentary sequence in southwestern USA¹. The results suggested the existence of a normal and reversed polarity sequence in rocks whose stability had been tested by thermal demagnetization. We have subsequently carried out a sedimentological study of these rocks, the results of which have changed our original conclusions.

Although haematite was found at nearly all grain contacts indicating that it was introduced early in the diagenetic history of these rocks, it is also found both as a staining on the secondary quartz overgrowths and in pore spaces. It is this latter secondarily formed haematite which forms the bulk of the haematite present and, we now believe, is primarily responsible for the remanence we measured.

This discovery led us to re-examine our previous results. The results from the Navajo Sandstone which provided differing results from the upper and lower parts of the section were from rocks which had been collected from two different parts of the Gunlock section (S. Utah) each with a characteristic dip. We have recomputed all the measurements with respect to the present horizontal, the closest approach to a fold test possible, and found that the difference in direction between the two sections was minimized with the virtual pole (8.72 N, 26.0 E, $\alpha=3.1$) not significantly different from the present geographic pole. We therefore feel that other Jurassic formations which provide similar virtual pole positions to those we originally calculated from the bedding plane position may similarly be suspect (Table 1).

We believe the magnetization of the immediately underlying Kayenta Formation is stable and represents the geomagnetic field direction of Upper Triassic times, for not only did we find the magnetization stable, but the directions are consistent with those of more fully investigated rocks of the same age

Table 1 Jurassic Virtual Pole Positions for North America

Formation	Sampling *	Decl.	Inc.	$\alpha 95$	K	Virtual pole		Reference
						Long.	Lat.	
Navajo Sandstone lower corrected to Jur. hor.	107S, 480 sp.	347.8	35.6	5.5	78.1	72.1 E	80.0 N	4
Navajo Sandstone upper corrected to Jur. hor.	69S, 280 sp.	13.1	49.4	3.5	196.9	5 W	81.8 N	4
Navajo Sandstone corrected to present hor.	176S, 760 sp.	1.8	54.3	3.1	113.5	36.0 E	87.2 N	4
Navajo Sandstone reversed	20 sp.	162.2	9.6	40.5	1.6	94.1 E	43.0 N	4
Kayenta Fm.	13S, 104 sp.	351.0	19.0	9.8	50.9	82.5 E	61.2 N	4
Kayenta Fm.	4S, 39 sp.	16.0	50.0	—	—	39.0 E	83.0 N	5
Carmel Fm.	9S, 31 sp.	349.0	63.0	14.0	11.0	160 W	80.0 N	5
Carmel Fm. correct to Jur. hor.	12S, 48 sp.	18.9	64.2	11.5	13.4	52.8 W	75.5 N	4
Carmel Fm. correct to present hor.	12S, 48 sp.	352.6	73.0	11.1	13.6	122 W	70.1 N	4

*S=sites; sp.=samples.

elsewhere. The discovery of the secondary magnetization of the Jurassic Navajo Sandstone removes the high rate of displacement which is necessary to explain the change between the virtual pole positions derived from the Kayenta and Navajo rocks.

The reversed directions of magnetization found in the Navajo Sandstone are dispersed; however, the virtual pole position calculated from them (274.1 E, 43 S, $\alpha=40.5$) differs little from that of the Kayenta Formation. It therefore appears to us that in these reversely magnetized samples we may be observing relicts of an original magnetization overprinted by a variable but small stable secondary magnetic component (of CRM type). It is probable that a similar situation may exist in the normally magnetized rocks, but is more difficult to discern.

The question of the time of origin of the apparently dominant normal direction of secondarily acquired magnetization is important in view of the rapidity of polarity reversals in the last few million years. We suggest the magnetization was most probably acquired during the Brunhes normal epoch when, owing to the strong climatic fluctuations of the Ice Age, water movement through the porous Navajo Sandstone was at a peak. This clearly implies a mobility of iron greater than is normally regarded to be the case. It is also clear that without a sedimentary examination the magnetization of porous rocks must be treated with some caution, and for this reason we regard our measurement on the Carmel Formation as suspect.

It is unfortunately true that the behaviour of the Jurassic geomagnetic field in North America still remains largely unknown, with the best results to date those of Symons² and Opdyke and Wensink³.

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Concentration of Suspended Particulate Matter in Surface Sea Water

A KNOWLEDGE of the kind and amount of suspended particulate matter in the World Ocean is important for the solution of a number of geological, geochemical and environmental problems. Varying estimates of total suspended particulate matter in sea water have been made and Lisitzin¹ and Gordeyev² report concentrations which, in some areas, are one or two orders of magnitude higher than those found by Ewing *et al.*^{3,4}

We present here the results of a recent study in which particulate matter was collected from surface water samples (0–5 m) from the Atlantic and Indian Oceans and the China Sea during March and July 1972. Collections were made on board MV Cyclops by pumping sea water from a position by the ship's bows (which minimized contamination from the ship's sides) via plastic tubing and filtering through weighed 0.45 μm membrane filters. The filters were washed with distilled water until salt-free, dried at 60°C to constant

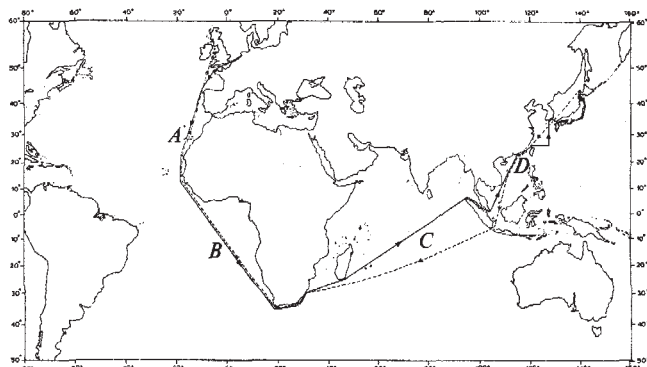


Fig. 1 The track of the MV Cyclops. —, UK-Japan run; ---, Japan-UK run. Average concentrations of total suspended matter in surface water are given for the major oceanic areas. A, 467 $\mu\text{g l}^{-1}$; B, 150 $\mu\text{g l}^{-1}$; C, 66 $\mu\text{g l}^{-1}$; D, 127 $\mu\text{g l}^{-1}$.

weight and the weight of particulate matter determined. The ship's route is shown in Fig. 1, and the results for the various oceanic areas are listed in Table 1. Some of the more important aspects of the study are discussed below.

Table 1 Concentration of Total Suspended Particulate Matter in Surface Sea Waters

Oceanic area	No. of samples	Range of concentration ($\mu\text{g l}^{-1}$)	Average concentration ($\mu\text{g l}^{-1}$)	Time of year
North Atlantic	25	121–1,168	467	April and July
South Atlantic	23	67–448	150	April and July
Indian	30	43–110	66	April and June
China Sea	22	29–338	127	May and June
Oceanic deep-sea average (including N. Atlantic)*	100	29–1,168	199	—
Oceanic deep-sea average (excluding N. Atlantic)	75	29–448	110	—
Java Sea	2	580–915	747	June
English Channel	4	796–2,609	1,719	March
Irish Sea	6	1,087–1,960	1,680	July
Inland Sea (Japan)	7	300–3,641	1,452	May
South Japanese coast	7	173–349	245	May–June
South African coast	11	84–1,530	456	April and June

* Two oceanic deep-sea averages are given because collections in the North Atlantic included some from near-shore waters.

Along the eastern margins of the North Atlantic Ocean the average concentration of suspended matter during April and July was 467 $\mu\text{g l}^{-1}$. Along a similar track Gordeyev² found an average of $\sim 1,000 \mu\text{g l}^{-1}$ in April, and Svirenk⁵ reported concentrations of 800–1,200 $\mu\text{g l}^{-1}$; both sets of determinations were made with 0.7 μm filters. Our values are lower than these, but are higher than the 40–150 $\mu\text{g l}^{-1}$ quoted for North Atlantic open-ocean surface water⁷. This is to be expected because our collections were made along the continental margins.

Our average value for the concentration of suspended matter in the open-ocean surface waters of the South Atlantic during April and July was 150 $\mu\text{g l}^{-1}$. This is considerably lower than the average of $\sim 800 \mu\text{g l}^{-1}$ found by Gordeyev² for surface waters in the same area in April, and approaches that of Jacobs and Ewing, who used a continuous centrifuge, and reported an average of $\sim 50 \mu\text{g l}^{-1}$ for open-ocean South Atlantic waters below a depth of 180 m. In open-ocean water of the tropical Atlantic Svirenk⁵ gave an average of $\sim 400 \mu\text{g l}^{-1}$ of suspended matter.

Jacobs and Ewing³ found an average of $\sim 71 \mu\text{g l}^{-1}$ in open-ocean Indian Ocean waters below 180 m. This is very close to our average of 66 $\mu\text{g l}^{-1}$ for open-ocean surface waters. In contrast, Lisitzin reported concentrations of 500–1,000 $\mu\text{g l}^{-1}$ in surface waters of the Indian Ocean.

The content of suspended matter in waters from the various near-shore localities, excluding those off the West African coast, ranges between 84 and 2,609 $\mu\text{g l}^{-1}$, with an average of 955 $\mu\text{g l}^{-1}$. These values are in the same range as those quoted by Svirenko⁵ who found an average of $\sim 1,500 \mu\text{g l}^{-1}$ suspended material in the English Channel.

Various factors affect the concentration of total suspended matter in sea water. For example, biogenous components fluctuate seasonally and are concentrated in certain areas, where upwelling occurs; and inorganic suspensions are affected in near-shore areas by river run-off, and in deep waters by processes such as lutite flows³. However, it may be concluded that in open-ocean surface waters in general, apart from those off the West African coast, the concentration of total suspended matter is in the range ~ 50 to $\sim 500 \mu\text{g l}^{-1}$, with an average of $100 \mu\text{g l}^{-1}$. These are considerably lower than the values usually quoted^{1,2,5,6} for open-ocean surface waters (range, ~ 100 to $>1,000 \mu\text{g l}^{-1}$), and may be compared to those given by Ewing *et al.*^{3,4,7} who find a range of <50 to $\sim 150 \mu\text{g l}^{-1}$ in open-ocean surface waters and <1 to $\sim 250 \mu\text{g l}^{-1}$ in clear open-ocean deep waters. In marginal seas, such as the Inland Sea (Japan), the average concentration of total suspended matter in surface water is apparently of the order of $\sim 1,500 \mu\text{g l}^{-1}$.

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Rheology of Oil Films at High Contact Pressures

WE report here a new approach to studying the shear behaviour of thin films of oil under conditions of elastohydrodynamic lubrication such as arise at points of contact in ball bearings or between gear teeth. During its passage through the contact the oil is rapidly compressed to pressures in the region of 10^4 bar and then sheared by the sliding motion of the metal surfaces. Hitherto this behaviour has been studied using rolling contact disk machines in which rollers having parallel axes are pressed into contact. Rolling motion generates an oil film of known thickness ($\sim 1 \mu\text{m}$) between the hard steel surfaces; superimposed sliding shears the film. At very small sliding speeds—shear rates—the behaviour is linear: the mean shear stress required to shear the film τ is proportional to the sliding speed. At higher sliding speeds the mean shear stress reaches a maximum (critical) value τ_c . It has been suggested² that the observed behaviour can be explained by the oil exhibiting viscoelastic properties at these high pressures, when the viscosity is known to increase by many orders of magnitude. Unfortunately this hypothesis cannot be tested with certainty by conventional disk machine tests, which do not distinguish unequivocally between viscous and elastic response of the fluid in the contact zone. We report here a different rolling

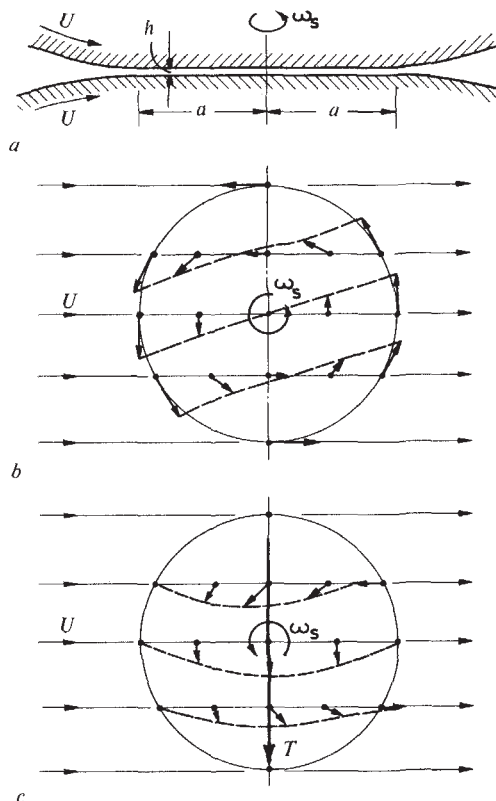


Fig. 1 Kinematics of rolling with spin for a circular contact region. a, The contact region. b, Slip velocities S . c, Slip displacements S .

contact experiment which reveals viscoelastic behaviour directly by separating elastic and viscous response of an oil film under elastohydrodynamic conditions.

The principle of the experiment is illustrated in Fig. 1. Two rollers having suitably curved profiles are pressed together by a force P such that, in the absence of lubricant, they would make contact over a circular area of radius a . They are rolled together with equal peripheral speeds U so that they generate an elastohydrodynamic film of thickness h . One surface is then given a small angular velocity of spin ω_s which shears the film as shown. Following a fluid element along any streamline through the "contact" region we see that it is sheared first in one direction and then in the other. This is the significant difference from the conventional disk machine experiment, in which the fluid is continually sheared in the same direction. A purely viscous fluid develops shear stresses in response to the shear rate vectors S (Fig. 1b). Clearly no net shear force will be exerted by the film in this case. An elastic film, on the other hand, will develop shear stresses in response to the total shear S experienced by the fluid elements. The total shear vectors are shown in 1c. Stresses developed in response to total shear give rise to a resultant force T acting perpendicular to the direction of rolling as shown. Thus a purely elastic film with constant shear modulus G would develop a shear stress GS/h . Integrating over the whole contact area gives

$$T = \frac{\pi}{4} \frac{Ga^4}{h} \frac{\omega}{U} \quad (1)$$

assuming that the solid surfaces do not deform in shear. In practice it is necessary to make a correction for the elastic deformation of the rollers.

The action of rolling combined with spin can be realized in several ways. We have used an apparatus designed by Poon and Haines³, shown diagrammatically in Fig. 2. The (upper) crowned roller rolls in contact with the (lower) cylindrical roller. Spin is introduced by tilting the axis of rotation of the upper roller through an angle α in a vertical plane, thus introducing an angular velocity of spin, $\omega \sin \alpha$. The upper roller is

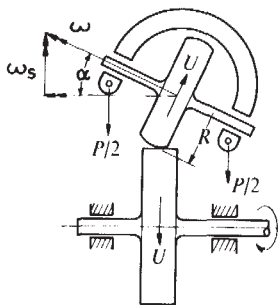


Fig. 2 Poon and Haines rolling contact apparatus. Angular velocity of spin, $\omega_s = \omega \sin \alpha$; peripheral rolling speed $U = \omega R$.

mounted on a cantilever spring dynamometer to measure the transverse force T .

Exploratory tests have been made on two mineral oils: Shell Vitrea 79 (viscosity: 8.9 poise at 30° C), Shell Turbo 33 (0.84 poise at 30° C) and a synthetic fluid, di-2-ethyl hexyl phthalate (0.45 poise at 30° C). Evidence of elastic behaviour was found with all three fluids at high pressure. It was most marked for Vitrea 79 which has been tested in more detail. Its response to shear appears to be almost completely elastic above a pressure of about 700 MN m⁻² (10⁵ lbf in⁻²) and above a rolling speed of 0.4 m s⁻¹. The magnitude of the transverse force T is observed to increase with $\sin \alpha$, linearly at first and then reaching a maximum of about 0.03 poise when $\sin \alpha \approx 20^\circ$.

If the response is fully elastic then equation (1) can be used to deduce a value for the mean effective shear modulus $\bar{G}$ of the fluid for various test pressures and speeds. The results are shown in Fig. 3, where it appears that $\bar{G}$ has values in the range 10²–10³ MN m⁻² which rise with pressure. The only independent measurements of the elastic modulus of lubricating fluids at high pressure have been made by Barlow *et al.*⁴ and Hutton and Phillips⁵ in which a pressurized sample of the fluid is subjected to high-frequency oscillatory shear. They find values of shear modulus which are about an order of magnitude higher than the values shown in Fig. 3. It must be borne in mind, however, that the fluids tested were different and that the pressure remains steady during the

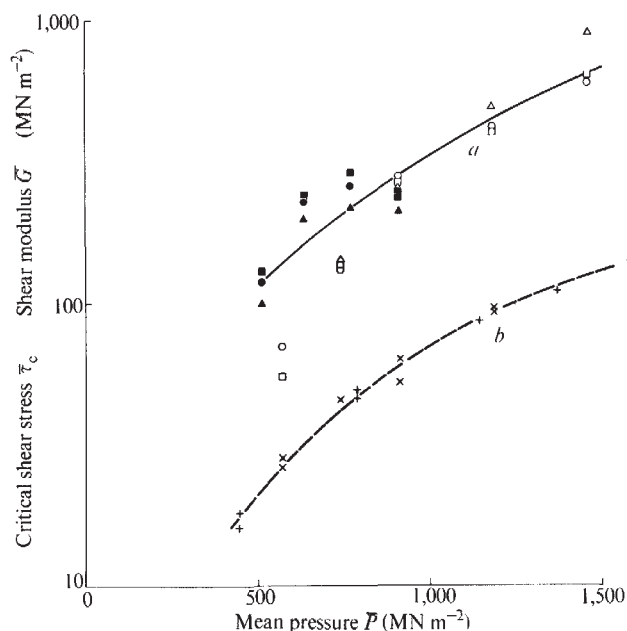


Fig. 3 *a*, Mean effective shear modulus $\bar{G}$ (Vitrea 79 at 25° C) deduced from rolling with spin experiments. $R = 25$ mm: $U = 0.40$ (○); 0.80 (□); 1.60 (△) m s⁻¹. $R = 39$ mm: $U = 0.40$ (●); 0.80 (■); 1.60 (▲) m s⁻¹. *b*, Mean critical shear stress $\bar{\tau}_c$ from Poon and Haines apparatus (x) and from disk machine (+).

oscillatory shear experiments, whereas it is very transitory (about 10⁻³ s) in the lubrication experiments.

In an earlier paper¹ it was suggested that the maximum shear stress observed in lubricated sliding might be due to shearing of the film in the manner of a plastic solid rather than a viscous liquid, when the shear stress reaches a critical mean value $\bar{\tau}_c$. This hypothesis seems even more probable if the film is behaving like an elastic solid at small strains. Values of $\bar{\tau}_c$ for Vitrea 79, obtained both in the disk machine and in the new apparatus, are also shown in Fig. 3. It will be seen that $\bar{\tau}_c \sim 0.2 \bar{G}$. It is striking that a similar proportional relationship between yield stress and elastic modulus is commonly found to hold for glassy polymers⁶.

We conclude from our new experiment that when a film of high viscosity mineral oil is subjected to small shearing strains under high pressure it exhibits "elastic" behaviour. At larger strains it is suggested that the film shears by a process of plastic flow.

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BIOLOGICAL SCIENCES

Release of Amino-acids and Neurosecretory Substances after Stimulation of Nerve-endings (Synaptosomes) isolated from the Hypothalamus

SYNAPTOSOMES prepared from the cerebral cortex by homogenization and density gradient centrifugation show a variety of metabolic properties characteristic of whole cells when incubated in suitable media^{1,2}. Increasing the potassium concentration of the medium or electrical stimulation caused a preferential calcium dependent³ release of the physiologically active amino-acids glutamate, aspartate and GABA⁴. Acetylcholine synthesized by synaptosomes was also released by K⁺ and electrical stimulation^{5,6}, and was also calcium dependent⁶. It has been shown⁷ that nerve-endings isolated from the median eminence of the hypothalamus contain corticotrophin-releasing factor (CRF) and antidiuretic hormone (ADH), and this study was undertaken to establish whether electrical and potassium stimulation would cause the release of neurosecretory substances and amino-acids from hypothalamic synaptosomes.

Hypothalami were collected from sheep stunned electrically and then killed by exsanguination. Pieces of hypothalamus including the median eminence, weighing about 500 mg, were removed within 5 min of death and placed in ice-cold 0.32 M sucrose. Synaptosomes were prepared by the method of Gray and Whittaker⁸ and suspended at a concentration of 3–6 mg protein ml.⁻¹ in Krebs phosphate medium containing 10 mM glucose. Electron microscopy showed that the major components of the preparation were nerve-endings about 1 μm in diameter, containing mitochondria and masses of dense-core osmophilic granules (100 nm in diameter) within an intact synaptosomal membrane. Suspensions (2.5 ml. containing

synaptosomes from 4–5 hypothalami per flask) were incubated at 37° C in Warburg respirometer vessels fitted with concentric gold ring electrodes. After 20 min incubation electrical pulses of alternating polarity (10 V amplitude; 0.4 ms duration; frequency 100 s⁻¹; average continuous current 10–15 mA) were applied to the suspension for a further 20 min period. Potassium stimulation was effected by adding medium containing 600 mM KCl from the side arm of the vessel to raise the final K⁺ concentration in the suspension from 5 to 55 mM. Unstimulated suspensions of synaptosomes from the same preparation served as controls.

The suspensions were centrifuged after incubation and CRF activity in the supernatants was measured using mice in which the release of endogenous CRF was blocked by pretreatment with chlorpromazine and sodium pentobarbitone (fluorimetric determination of the increase in adrenal corticosteroids represented the end-point of the assay). This is essentially the method described by Cheifetz⁹ except that codeine was omitted from the pretreatment. Vasopressor activity was determined in male rats pretreated with dibenamine and anaesthetized with urethane¹⁰. ACTH was assayed by the adrenal response in hypophysectomized rats¹¹ and by radioimmunoassay using an antiserum to α 1-24 ACTH.

Electrical and K⁺ stimulation produced a marked increase in the rate of respiration similar to that described previously¹. There was no significant difference between the respiratory rates of synaptosomes prepared from the cerebral cortex and those from the hypothalamus.

Table 1 Release of CRF by Synaptosomes Prepared from the Sheep Hypothalamus

	Hypothalamus	Cortex
Unstimulated	2.4 ± 0.3 (9)	0.8 ± 0.2 (6)
Electrical stimulation	11.4 ± 0.9 (10)	2.3 ± 1.2 (6)
K ⁺ stimulation	6.6 ± 0.6 (4)	0.7 ± 0.2 (4)
Control injection of HCl extract from:		
1 rat stalk-median eminence (6 mg)	13.6 ± 2.3 (5)	
Equivalent weight of rat cortex	1.9 ± 1.7 (5)	

Values are expressed as the difference in corticosteroid content of adrenals (μ g g⁻¹) between mice injected with 0.3 ml. supernatant from incubated synaptosomes and controls given 0.3 ml. of incubation medium from the same experiment. Control values for rat tissue extracts showed increase in adrenal corticosteroid content over saline injected controls. (Mean $\pm$ s.e.; number of experiments in parentheses.)

There was a substantial release of CRF following the electrical stimulation of synaptosomes from the hypothalamus (Table 1). The response obtained from 0.3 ml. supernatant (containing 1–2 mg of nerve-ending protein before centrifugation) was similar to that obtained after the injection of the neutralized HCl extract of one rat stalk-median eminence. A reduced but still significant response was obtained after potassium stimulation. Control injections of the high K⁺ medium caused only a slight increase in the level of adrenal corticosterone and did not interfere with the assay.

The unstimulated preparations of hypothalamic synaptosomes also gave a response in the assay, which suggested that perhaps a small proportion were damaged and losing CRF to the incubation medium. Cortical nerve-endings incubated under identical conditions at the same protein concentration did not produce a significant effect in the absence of stimulation; stimulation with electrical pulses but not potassium produced a significantly increased response. This activity, however, was only equivalent to the levels for the unstimulated hypothalamic nerve-endings. The difference in the response obtained with stimulated cortical and hypothalamic synaptosomes thus resembled that produced by control injections of HCl extracts of the original tissues (Table 1). No ACTH was detectable in the supernatants and it was concluded that the responses obtained in these experiments were due to a specific corticotrophin releasing factor. This was confirmed by experiments in which halved anterior pituitary glands were incubated *in vitro* with

the supernatants and ACTH release measured by radioimmunoassay. Only stimulated preparations of hypothalamic synaptosomes caused ACTH release from the incubated pituitaries.

Electrical stimulation caused the release of vasopressin. Levels measured in the unstimulated medium were variable, ranging from undetectable to 15 mU ml.⁻¹, the average being 2 mU ml.⁻¹. On stimulation there was a consistent increase to 23 $\pm$ 8 mU ml.⁻¹ (mean $\pm$ s.e.; five experiments) and that this pressor activity was due largely to ADH was shown by inactivation with 0.1 M thioglycollate and confirmed by the inhibition of diuresis produced in ethanol anaesthetized, water loaded rats. The amount of ADH released by stimulation was considerably below the dose (60 mU) causing release of ACTH in the CRF assay⁹.

Further confirmation that hypophysiotrophic substances were being released from hypothalamic synaptosomes by electrical stimulation was obtained when the supernatants were tested for prolactin-inhibiting factor (PIF). Halved anterior pituitary glands from female rats were incubated in Krebs–Ringer bicarbonate medium containing 5 mM glucose, and prolactin release was measured by radioimmunoassay.

The results of three experiments are shown in Table 2. PIF activity was present in the supernatants from stimulated hypothalamic synaptosomes. Inhibition was not obtained from unstimulated preparations and the levels of prolactin secretion were similar to those obtained from control pituitary incubations to which an equal amount of the phosphate medium was added. Stimulated suspensions of nerve-endings from the cortex were without effect on the secretion of prolactin.

In view of previous observations that a preferential release of physiologically active amino-acids was produced by stimulation of cortical synaptosomes^{3,4} the pattern of amino-acid release from the hypothalamic preparations was examined (Table 3). Although rat hypothalamus showed a release pattern similar to that previously found for rat cortex⁴, both cortex and hypothalamus from sheep showed much reduced or virtual absence of the preferential release of aspartate, glutamate and

Table 2 Release of PIF by Synaptosomes Prepared from the Sheep Hypothalamus

	Unstimulated	Electrical stimulation	Inhibition %
Experiment 1	114.4 $\pm$ 8.4	73.2 $\pm$ 8.4	32.4 $\pm$ 9.4
Experiment 2	124.8 $\pm$ 10.2	77.6 $\pm$ 3.8	36.1 $\pm$ 6.6
Experiment 3	62.8 $\pm$ 3.7	50.4 $\pm$ 2.2	19.7 $\pm$ 4.5

Values, determined by radioimmunoassay, are expressed as prolactin secreted (ng mg⁻¹ pituitary) during a 1 h test period in which 0.5 ml. supernatant was added to 1.5 ml. incubation medium in each flask. Mean $\pm$ s.e. of 5 paired flasks in each experiment.

Table 3 Release of Amino-acids after Electrical Stimulation of Nerve-endings isolated from Cerebral Cortex and Hypothalamus of Rat and Sheep

	Rat (phosphate medium)		Sheep (phosphate medium)		Sheep (bicarbonate medium)	
	Cortex*	Hypo- thalamus	Cortex	Hypo- thalamus	Cortex	Hypo- thalamus
Aspartate	59 $\pm$ 4	53 $\pm$ 6	5 $\pm$ 2	7 $\pm$ 3	52 $\pm$ 6	30 $\pm$ 3
Glutamine	30 $\pm$ 2	16 $\pm$ 3	2 $\pm$ 2	14 $\pm$ 3	3 $\pm$ 1	-2 $\pm$ 1
Serine	24 $\pm$ 3	4 $\pm$ 1	-1 $\pm$ 1	9 $\pm$ 3	4 $\pm$ 2	7 $\pm$ 8
Glutamate	62 $\pm$ 7	56 $\pm$ 6	6 $\pm$ 2	18 $\pm$ 3	56 $\pm$ 8	30 $\pm$ 3
Glycine	31 $\pm$ 3	27 $\pm$ 1	2 $\pm$ 1	10 $\pm$ 5	8 $\pm$ 2	1 $\pm$ 1
Alanine	28 $\pm$ 3	18 $\pm$ 3	4 $\pm$ 2	10 $\pm$ 3	6 $\pm$ 2	-1 $\pm$ 2
GABA	58 $\pm$ 7	65 $\pm$ 7	3 $\pm$ 2	3 $\pm$ 1	62 $\pm$ 7	57 $\pm$ 11
No. of experiments	10	6	8	6	7	7

* Data from ref. 3.

The percentage of total amino-acid released to the medium by stimulation is corrected for amino-acid released during incubations without stimulation, Means $\pm$ s.e.

GABA, though pool sizes of these amino-acids were comparable in the two species. When the sheep synaptosomes were incubated in Krebs-bicarbonate medium instead of the phosphate medium, the medium calcium level being maintained at 0.75 mM, the preferential release of these three physiologically active amino-acids was obtained. It seemed likely that this difference was due to the reduced availability of calcium in the phosphate medium inhibiting release. Titration methods have shown that as much as 65% of calcium would be present as a non-ionic soluble phosphate complex in the phosphate buffered medium¹³. The importance of adequate calcium levels for the amino-acid release from hypothalamic synaptosomes was confirmed by omitting calcium or by adding 1 mM EGTA to the bicarbonate medium both of which blocked the release of aspartate, glutamate and GABA.

It would appear from our results that nerve-endings isolated from the sheep hypothalamus contain CRF, PIF and perhaps all of the hypophysiotrophic factors which control the secretion of hormones by the anterior pituitary gland. They also contain the neurohypophysial hormone vasopressin and presumably oxytocin as well, although the presence of the latter was not looked for in these experiments. Preliminary experiments indicated that the amounts of the hypophysiotrophic factors released by stimulation were greater than the levels which can be extracted from an equivalent weight of hypothalamic tissue using the standard HCl extraction procedure. Because of the lengthy (5 h) procedure involved in the preparation of synaptosomes, it is surprising that such relatively high levels of CRF are present in the nerve-endings. The possibility of *de novo* synthesis of this and related small polypeptides cannot be excluded at present, especially in view of reports that synaptosomes from the cerebral cortex were able to synthesize proteins¹⁸ and phospholipids¹⁴.

If the release of CRF and related substances is triggered by depolarization of the isolated nerve-ending, and this is comparable to the physiological stimulus for the release of such factors, then the techniques described here provide a new *in vitro* approach to the study of some fundamental aspects of neurosecretory processes. It may be possible, for example, to determine whether the inhibitory feedback action of adrenal corticosteroids on the release of ACTH is mediated through mechanisms involving inhibition of synthesis or inhibition of release of CRF and this possibility is being investigated at the moment.

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Locating Protein in Membranes

PROTEIN molecules associated with membranes presumably are the keys to the mechanisms of a number of cell functions. For two membranes it has been suggested¹ that some of the protein is embedded in a lipid bilayer. I present here evidence of two kinds, covering a wide variety of natural membranes, for molecules of protein each partly inserted in a lipid bilayer and partly exposed to the aqueous medium outside. This evidence generally rules out a normal lipid bilayer with all the protein outside.

If all membranes contained a continuous bilayer of lipid with the protein at the surfaces, the average thickness of solids would be greater the larger the proportion of protein. This was tested, using X-ray diffraction data for a lipid bilayer²⁻⁴ and some natural membranes⁵⁻¹⁰ with a wide range of lipid-to-protein ratios. Thus, knowing a periodicity of membrane stacking and subtracting the proportion by volume for water, I have calculated an average thickness for the solids in each membrane (Table 1). For the membranes listed in Table 1 the average solids thickness does not increase in proportion to the protein content, contradicting the general model having a lipid bilayer with all the protein outside, whether as dense layers or globular molecules.

The average thickness for the lipids in a membrane can be defined as the product of the average solids thickness and the volume fraction for lipid. For the membranes listed in Table 1 there seems to be a thinning of the lipids as the protein content increases. At the same time, the X-ray diffraction patterns recorded from a number of natural membranes^{1,5-11} all indicate electron-density profiles with two peaks, and each peak probably locates a layer of the electron-dense head-

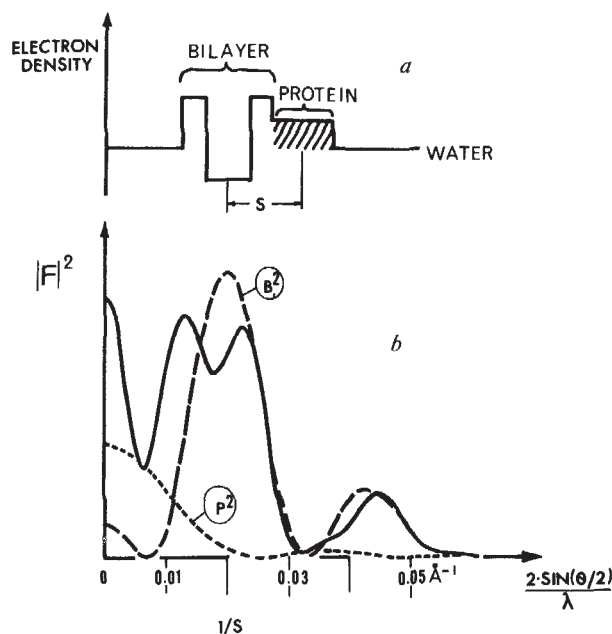


Fig. 1 *a*, Simplified electron-density profiles for a bilayer and, to the right, a layer of protein. The two bilayer peaks, their centres separated by $D=40$ Å, locate electron-dense lipid head-groups and the trough between, the fatty chains. *b*, The corresponding squared Fourier transforms, F^2 , versus $2 \cdot \sin(\theta/2)/\lambda$ where θ is the diffraction angle and λ is the X-ray wavelength. In each case the diffracted X-ray intensity will be proportional to F^2 (ref. 1). The dashed curves (---) are for the bilayer (B^2) alone and (---) for the protein layer (P^2) alone. The solid curve, for the two together, oscillates above and below B^2 , showing cross interference between the two structures¹⁹. The frequency of oscillation is a measure of the distance S ($=50$ Å here). If protein molecules were to be centred in one or both of the bilayer-profile peaks ($S=D/2$), the oscillations above and below B^2 would not be obvious since they would coincide in frequency with the bilayer (B^2) bands¹⁹.

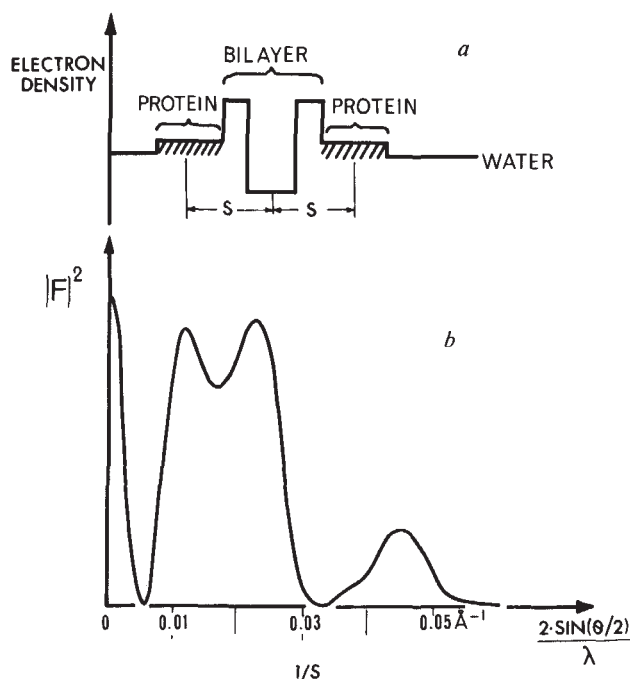


Fig. 2 a, The same amount of protein as in Fig. 1a is distributed equally on both sides of the bilayer, for example, protein molecules packed only half as densely. b, The corresponding F^2 curve is closely similar to the solid curve in Fig. 1b. This illustrates that beyond $0.01 \text{ \AA}^{-1}$ protein contributes mainly to cross interference, which is the same for protein on either bilayer surface¹⁹.

groups of the lipids^{1,5-12}. The values given in Table 1 for the peak-to-peak distances on the profiles are, however, like the solids thicknesses, roughly constant; these distances evidently measure the total membrane substance rather than the lipids alone. To resolve the apparent contradiction it has been suggested¹ for the erythrocyte and visual cell disk membranes that some of the protein is inserted in a bilayer of the lipids. This arrangement is now all the more clearly indicated for the purple membrane since the average lipid thickness is only $15 \text{ \AA}$.

A more direct test of structure is the diffracted X-ray intensity recorded from membranes in dispersion. The predicted effect of adding layers of protein outside a lipid bilayer is illustrated in Figs. 1 and 2 (see also ref. 11, Fig. 1c). The low-angle X-ray diffractions recorded from a wide variety of natural membranes are not those that I predict¹⁹ for protein molecules at the surfaces of a normal lipid bilayer. In contrast the predicted change, Figs. 1 and 2, has been observed¹⁹ after the addition of cytochrome *c* to a sonicated dispersion of Asolectin lipids. I conclude that the X-ray patterns recorded from a number of natural membranes are not those expected for the Davson-Danielli¹³, and similar¹⁴, models of structure.

The X-ray results are consistent with a model in which globular protein molecules are each partly submerged in a

lipid bilayer. The lipid fatty chains and a part of each protein molecule together form a hydrophobic layer, which will prevent free movement of solute molecules—perhaps the universal function of membranes. The model is indicated most decisively for the purple membrane since there is a $15 \text{ \AA}$ lipid thickness and only one species of protein molecule¹⁰. Thus the lipid headgroups can be located in layers $40 \text{ \AA}$ apart¹² only if a large part of each protein molecule is inserted into the bilayer. This model is least certain for myelin because of a low protein content and some uncertainty as to the water content. A model of this kind has been proposed for the visual cell disk membrane^{15,16}.

To associate in this way with lipid fatty chains a protein molecule must be polarized: on one face mainly the less electron-dense¹⁸ hydrophobic amino-acid side chains are exposed. Most of the more electron-dense¹⁸, hydrophilic residues will face the aqueous medium. The consequent asymmetry in the electron-density profile of the single protein molecule has been included in model profiles for the disk membrane^{12,17} and the purple membrane¹². The model also is compatible with the high degree of hydrophobicity¹⁸ of rhodopsin and the purple protein¹².

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Lymphocytes, Hormones and Ageing

THE suggestion that ageing may depend on immunological disorders¹⁻⁶ has been prompted by observations that organs and physiological systems show wide differences in the time they need to use up their "quota of cellular programme". Because the immunological system is fundamental for survival, if its function declines before other body functions, it would be a major determinant in the ageing processes.

We emphasize here the possible importance of the thymus as a biological clock and of hormones for the ageing processes of the lymphoid system. We also evaluate the capacity of lymphocytes, whose formation depends on hormones^{7,8}, to prevent early death and ageing processes. The experimental animals used are hypopituitary dwarf mice whose life-span under conventional conditions is only 3-5.5 months, and who are therefore more convenient in studies on ageing than normal mice.

Table 1

Membrane	Lipid: protein (wt : wt)	Average solids ‡ thickness (Å)	Average lipids ‡ thickness (Å)	Peak-to-peak distance on profile (Å)
Egg lecithin ^{1,4}	100% : 0%	40-45 *	40-45	35-40
Myelin ^{5,7}	75% : 25%	40-50 †	35-40	45
Visual cell disk ^{8,9}	40% : 60%	55	26	40
Purple ¹⁰	25% : 75%	49	15	40

* Depending on water content; similar values are found for other natural mixtures of lipids³.

† Assuming water content of 40-50% (see ref. 7, pp. 559-60).

‡ Using partial specific volumes of 1.0 ml./g for lipid and 0.75 ml./g for protein.

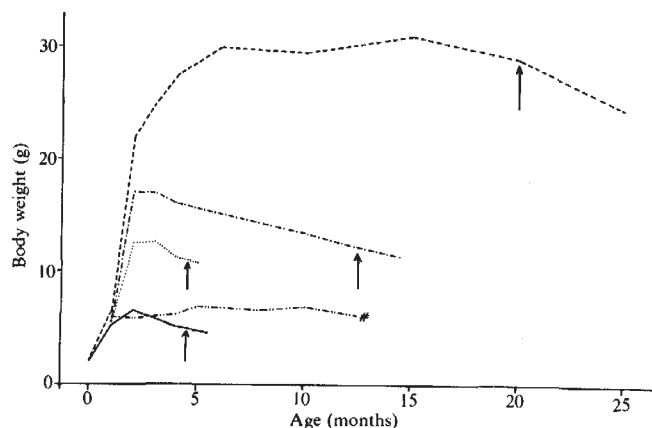


Fig. 1 Lymphocyte-dependent prolongation of life-span in early ageing Snell-Bagg dwarf mice. Dwarf mice (— · —) transplanted at 30 days of age with 150×10^6 peripheral lymph node lymphocytes from 40-day-old normal mice survive much longer than the untreated group (—). Dwarf mice (— · —) treated for 30 days in their post-weaning period with 250 μ g growth hormone and 1 μ g L-thyroxine show similar prolongation of life-span. Such a prolonged survival is not achieved if dwarf mice are thymectomized at young adult age before the beginning of the hormonal therapy (...). Normal Snell-Bagg mice survival (---). Arrows indicate mean life-span. Dwarf mice treated with lymphocytes have been killed before natural death; therefore the mean life-span has not been evaluated (#).

Dwarfism in Snell-Bagg mice is due to a recessive gene expressed phenotypically only in the homozygous condition. Dwarf mice show juvenile body proportions, reduced body size, low muscular activity, sterility, juvenile type of hair. These symptoms are either directly or indirectly the consequences of the endocrine deficiency of dwarf mice. The adenohypophysis is affected primarily⁹. Growth hormone (somatotrophic hormone) and thyrotrophic hormone producing cells are very scanty and sometimes even absent¹⁰. The total content of somatotrophic hormone (STH) in pituitary glands of dwarf mice is 1 : 1,000 of normal animals¹¹.

These endocrinological deficiencies also prevent the normal development of the lymphoid system. There is a marked hypotrophy of the thymus with progressive loss of small lymphocytes in the cortex; hypotrophy of spleen and peripheral lymph nodes, particularly in their thymus-dependent areas; decreased number of peripheral blood lymphocytes; and marked deficiency of cell-mediated immune reactions¹².

Treatment of dwarf mice with STH and thyroxine can induce a complete maturation of the lymphoid system; this most likely occurs through normalization of thymus structure and function. In agreement with this, normalization of cell-mediated immunity is also achieved by injection of mature lymphocytes⁸.

The parameters of ageing used were (1) life-span, (2) greying and loss of hair, (3) cutaneous and subcutaneous atrophy, (4) bilateral cataract, (5) *in vivo* cellular turnover measured by ^3H -thymidine uptake in different organs 24 h after an i.p. injection with $0.8 \mu\text{Ci g}^{-1}$ body weight, (6) percentage of growing spleen and kidney fragments in tissue culture¹³, (7) percentage of mitosis in outgrowing fragments of spleen and kidney. Although any one of these items may not be a decisive criterion of early ageing, taken together they serve as an indicator.

Fig. 1 shows the mean life-span of normal and dwarf mice: 20 months for normal animals and 4.5 months for dwarf mice. The mean body weight of normal and dwarf mice clearly confirms the well-known impairment of growth of dwarf mice.

With advancing age, characteristic alterations of the external appearance in dwarf mice occur. In the last two months of life, hairs start to become discoloured and to fall out, especially from the face (Fig. 2a). This process is accompanied by atrophy of the skin with progressive reduction of thickness and loss of normal elasticity. Bilateral cataract is also often present. Such symptoms occur in normal mice only in the last 3–4 months of their life. The uptake of ^3H -thymidine in normal animals is

progressively reduced with advancing age (Fig. 3). The difference between the one-month and 5-month-old dwarf mice is similar to that observed between one-month and 18-month normal mice.

Fragments from young dwarf mice grow as fast as do fragments from normal littermates, and those of 5-month-old dwarf mice give a pattern similar to those of old normal animals. The above observations are confirmed by the elevation of colchicine blocked mitosis in outgrowing spleen or kidney fragments. Details will be reported elsewhere.

Taken together these data strongly suggest that dwarf mice can be considered to be much older than their chronological age. The process of ageing in these animals is precocious and accelerated.

The prevention of ageing by lymphocytes was tested. Dwarf mice, treated at 30 days with a single i.p. injection of 150×10^6 peripheral lymph node lymphocytes from 40-day-old normal Snell-Bagg mice, survived for more than 12 months (Fig. 1). Although animals did not grow (Fig. 1), the usual loss of weight after the first two months of life was prevented. Dwarf mice treated with lymphocytes did not show the above external symptoms of the old untreated dwarf mice but looked normal (Fig. 2b). The cell turnover, as evaluated by ^3H -thymidine uptake in many of the tissues of 7-month-old animals (Fig. 3), is maintained at the level of young dwarf mice. Also *in vitro* the percentage of mitosis in outgrowing spleen and kidney fragments is similar to that observed in young dwarf mice.

In contrast to lymph node lymphocytes, one injection with thymocytes (150×10^6) or bone marrow cells (50×10^6) from 40-day-old normal Snell-Bagg mice were ineffective in ageing prevention.

To test the effects of hormones on ageing, dwarf mice were treated in the postweaning period with 250 μ g bovine STH and

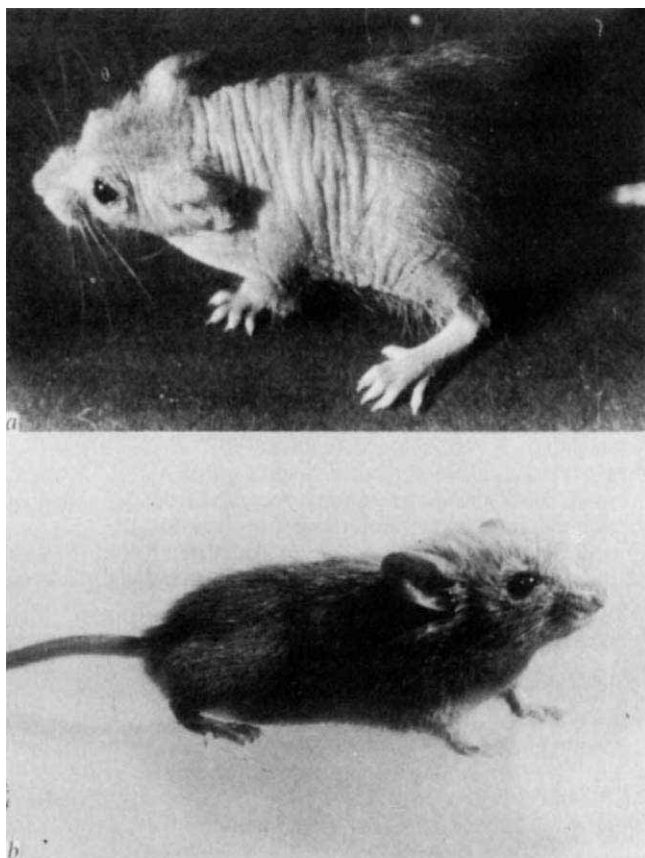


Fig. 2 a, External aspect of 4-month-old Snell-Bagg dwarf mouse. Note greying and loss of hairs, with cutaneous and subcutaneous atrophy. b, 7-month-old dwarf mouse after receiving one i.p. injection at 20 days of age with 150×10^6 lymph node lymphocytes from 40-day-old normal Snell-Bagg mice. All signs of ageing are prevented.

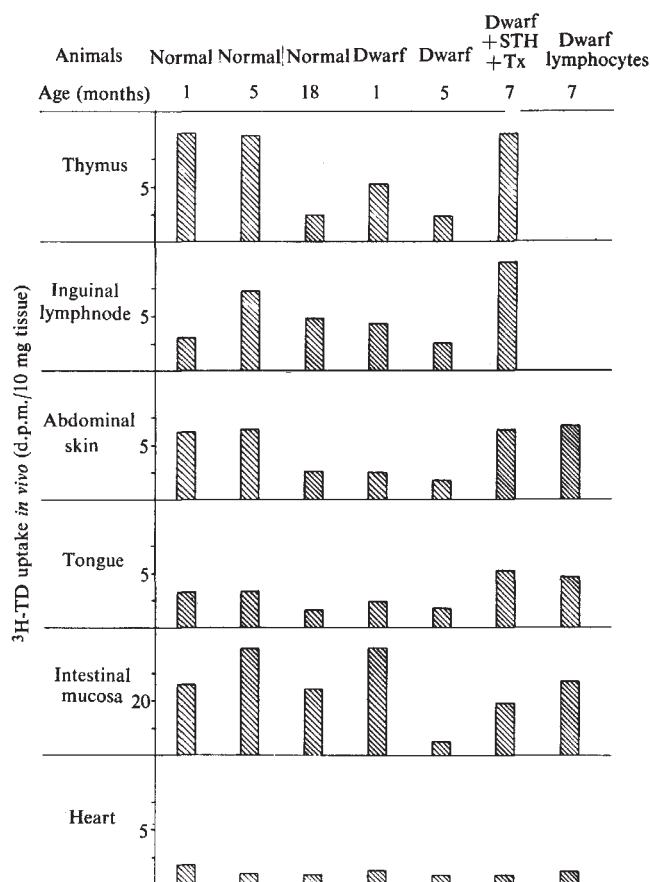


Fig. 3 ³H-thymidine (³H-TD) uptake in different tissues of mice injected with 0.8 μ Ci/g body weight 24 h before sacrifice. Radioactivity was measured in a Tricarb liquid scintillator spectrometer and counts were corrected for quenching and expressed as d.p.m./10 mg tissue. Old Snell-Bagg mice show a decreased thymidine incorporation compared with adult or young animals and a similar decrease is present in 5-month-old dwarf mice when compared to the 1-month-old group. Dwarf mice treated in their postweaning period for 30 days with 250 μ g growth hormone and 1 μ g thyroxine behave at 7 months as do adult normal animals.

1 μ g L-thyroxine for 30 days. Their life-span was prolonged to 12–14 months instead of the usual 5 months (Fig. 1) and their external appearance was similar to that of normal littermates. ³H-thymidine uptake at 7 months of age (Fig. 3), growth potential and the percentage of mitosis in spleen and kidney fragments cultured *in vitro* were also normal.

The delay in the onset of ageing symptoms and the prolongation of life-span in hormonally reconstituted dwarf mice was not achieved when thymectomy in young adult age preceded the hormonal therapy (Fig. 1).

The lymphoid system of the dwarf mice, because of the endocrine deficiency, is not fully developed and the life-span is drastically shortened. The full development of the thymus and the thymus-dependent lymphoid cells which can be induced by hormonal treatment in the postweaning period results in the prevention of early ageing and considerable prolongation of life. Adult normal lymph node lymphocytes transplanted into young dwarf mice are similarly effective. From these data one could deduce that intrinsic environmental factors, such as hormones, determine the functional level of the thymus and through its main cellular product, the lymphocyte, control the ageing processes. Therefore we wish to propose with Burnet² that the thymus might be considered as an important organ for ageing control of body tissues. One could predict then that the longer the thymus functions at its optimal level either as producer of humoral factors and/or lymphocytes, the longer will be the life-span.

The way in which lymphocytes might prolong life and

prevent ageing is far from clear. The most obvious but in our view insufficient explanation is that these thymus-dependent cells act in a strictly immunological sense in recognizing and reacting with foreign matter such as viruses, bacteria or modified self components. While such immunological surveillance is likely to play an important part in life prolongation it does not explain prevention of ageing parameters by lymphocytes. The interpretation we prefer at the present is that lymphocytes can recognize, besides foreign matter, microenvironmental changes, represented by modified host cells or their products. This could result in the cleaning up of such cells and in the release of stimulatory mediators, related to lymphokines, leading to normalization of the area. This view is supported by the experiments on the impairment of the regeneration of liver after adult or neonatal thymectomy^{14–16}.

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Tumours of the Nervous System in Mice treated Neonatally with N-Ethyl-N-nitrosourea

TUMOURS of the nervous system are readily induced in rats by a single transplacental or neonatal exposure to certain chemical carcinogens. This suggests that such tumours in man could well be the result of exposure to chemical carcinogens during foetal or early life. Druckrey *et al.* have studied nervous system carcinogenesis in rats using the nitrosamide N-ethyl-N-nitrosourea, $C_2H_5N(NO)CONH_2$ (ENU), administered both transplacentally^{1,2} and to newborn or very young animals³. Our own experiments with ENU administered to day-old rats⁴ agreed with these results in that a single 10 mg kg⁻¹ dose was sufficient to induce neural tumours in nearly 100% of treated animals, but differed in that in our rats a much higher proportion of tumours occurred in the brain rather than in the peripheral nervous system.

There has been little work in other species, but neural tumours have been induced in the rabbit⁵ and the dog⁶ using repeated administrations of N-methyl-N-nitrosourea. Treatment with these carcinogens has not induced tumours of the nervous system in mice. Methylnitrosourea administered to adult mice gave rise to thymic lymphomas⁷. Mice treated neonatally developed lymphomas⁸ or lymphosarcomas⁹, and intracerebral inoculation resulted only in leukaemia and lung tumours¹⁰. ENU administered to female mice at about the 16th day of pregnancy resulted in multiple lung tumours in the offspring but no neural tumours¹¹, though evidence of CNS damage was noted.

We have examined this apparent resistance of the murine nervous system to nitrosamide carcinogens. The effects of administering a range of doses of ENU to newborn mice of the four pure-line strains at present maintained in our laboratories, A, C57BL, IF and DBA/Bcr, were studied. We have now observed a number of nervous system tumours which are believed to be the first induced in mice by a systemically acting carcinogen.

Sixteen day-old litters of each strain were injected subcutaneously with a saline solution of freshly dissolved ENU at doses of 10 to 160 mg kg⁻¹ body weight. The volume injected was 0.02 ml. g⁻¹ body weight, and controls were treated similarly with normal saline. The final number of mice used were 113 of strain A, 94 C57BL, 88 IF and 104 DBA/Bcr. Mice were weaned at 3–4 weeks old (or later if necessary) and were maintained on 'Thompson cube diet 42' and tap water *ad lib*. Whenever possible animals showing evidence of tumours were killed for histological examination. Material, including the nervous systems of the affected animals, was fixed in formalin: acetic acid: methanol mixture (1:1:8), embedded in paraffin wax, and sections were stained by routine staining techniques.

Nervous system tumours have been found in ten mice, particulars of which are summarized in Table 1. These tumours gave rise to less visible disturbance than those seen in rats despite the considerable size of some of the lesions, as only four of the ten mice showed any degree of hind limb paralysis, and in two of these it was only slight.

The tumours can be allocated to two groups, those in the hindbrain arising between 20 and 28 weeks, and those in the peripheral nervous system, of which the first was found in a high-dose mouse at 40 weeks. There may be tumours in the animals still surviving, and a detailed report will be submitted later.

Although comparable numbers of mice of each strain were used, the ten mice with neural tumours belonged to only two of these, five IF and five DBA. Even these tumours have developed in only a small proportion of the animals at risk but thymic or splenic lymphomas have occurred in larger numbers. At this stage, A and C57BL mice appear to be resistant to neural carcinogenesis by nitrosamides, like those strains used by other workers^{7–11}.

Table 1 Nervous System Tumours in Mice treated Neonatally with N-Ethyl-N-nitrosourea

Strain	Sex	Mouse Dose mg kg ⁻¹	Age at death in weeks	Location	Tumours Type
DBA	M	80	20	Cerebellum	Oligoastrocytoma
IF	M	80	20	Cerebellum	Medulloblastoma
IF	M	80	27	Cerebellum	Medulloblastoma
IF	M	80	28	Cerebellum	Medulloblastoma
IF*	M	120	40	Cranial nerve	Schwannoma
				Brachial nerve	Schwannoma
IF	F	120	41	Sciatic nerve	Neurofibrosarcoma
DBA	F	40	50	Cranial nerve	Neuroblastoma/ Schwannoma
DBA	F	40	57	Spinal nerve	Schwannoma
DBA	M	10	69	Spinal nerve	Schwannoma
DBA	M	20	69	Spinal nerve	Schwannoma

* This mouse also had deposits of hepatocarcinoma in the liver.

The location of the four brain tumours is interesting. All were situated in the cerebellum, three of these being medulloblastomas. All these were male mice which had received ENU at 80 mg kg⁻¹. This high proportion of cerebellar tumours again contrasts sharply with results obtained in rats^{1–4} and suggests that IF or DBA mice, or their hybrids, may provide a useful experimental model for the study of these tumours. We believe the experimental medulloblastomas obtained will help to clarify the controversial question of the origin of these tumours in man.

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The Suppression of Non-specific Esterase Activity in Mouse Skin Sebaceous Gland by "CS" Gas

IN spite of the widespread use of the compound *o*-chloro-benzylidenemalononitrile (CS)^{1–5} as a riot control agent there appears to be no published data on its carcinogenic activity^{6–7}, although the usefulness of CS as a riot control agent has been stressed because of the relatively wide margin between effective and toxic doses⁶.

We report here testing of CS with a rapid bio-assay system which has been used as a predictive screening test for carcinogenesis. This bio-assay system involves the application of the test compound to mouse skin, followed by the evaluation of the area of skin sebaceous gland non-specific esterase activity^{8–9} which can be accurately and rapidly obtained with an image analysing computer. The application of well-known carcinogens and tobacco condensates to mouse skin causes suppression of sebaceous gland non-specific esterase activity whereas the non-carcinogens and irritants, so far tested, do not possess this ability. The degree of suppression has also been found to correlate with the known potency of the carcinogenic compounds.

CS is known to react readily with thiol groups at nearly neutral pH (refs. 10–12). As this reaction could account for the suppression of non-specific esterase activity, the related $\alpha\beta$ -unsaturated compounds cinnamionitrile and cinnamaldehyde were also included in the experiments. The reactivity of these $\alpha\beta$ -unsaturated compounds with the thiol, glutathione, was in the order CS $\geq$ cinnamaldehyde $\geq$ cinnamionitrile.

Groups of eight CFLP female mice, a hysterectomy-derived strain of Swiss origin 50 day old at start of treatment, when the hair growth cycle is in the telogen phase, were painted on

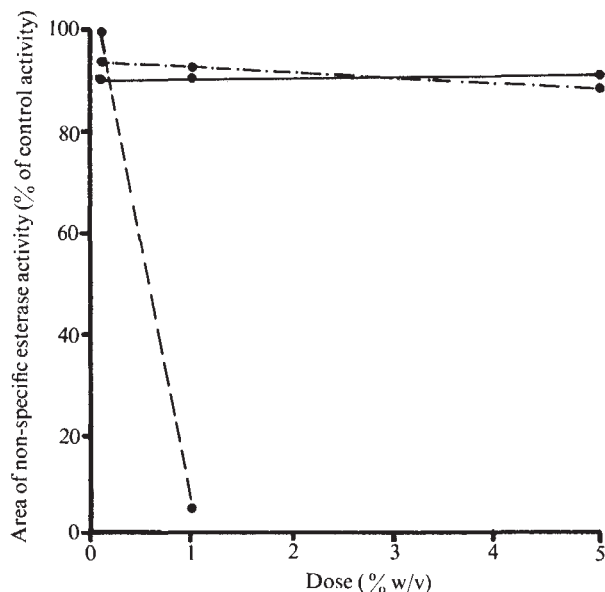


Fig. 1 Behaviour in the non-specific esterase test of cinnamonnitrile (●—●), cinnamaldehyde (●— · — · —●), and CS (●— · — · —●).

three consecutive days with either cinnamonnitrile, CS or cinnamaldehyde at 5%, 1% or 0.1% concentrations in acetone. A control group of sixteen mice were treated with acetone alone. Three days after the final application all the mice were killed and a piece of skin from the centre of the painted area was excised and frozen in hexane pre-cooled to -75°C .

The skin samples were mounted on cryostat tissue holders, and three 22 μm transverse sections at 110 μm intervals were cut from each skin sample on a 'Bright's' cryostat at a cabinet temperature of -25°C . The sections were air-dried at 6°C and fixed in formal calcium gum sucrose. Non-specific esterase activity was demonstrated in the sections by the method of Holt¹³ using 5-bromoindoxyl acetate as substrate.

Sections of skin from every group were included in each incubation procedure to allow subsequent correction for incubation variation. The sections were then mounted in 90% (w/v) aqueous solution of polyvinylpyrrolidone. The area of non-specific esterase activity in the sebaceous glands, as indicated by the reaction product, was measured in each skin sample using a 'Quantimet B' image analyser (Image Analysing Computers Ltd, Melbourne, Royston, Herts).

The results (Fig. 1) show that of the three $\alpha\beta$ -unsaturated compounds examined only CS suppressed non-specific esterase activity. Because the relatively reactive cinnamaldehyde did not suppress the enzyme activity, reactivity with thiol groups alone does not explain the marked suppression caused by CS when applied to mouse skin at 1% and 5% (w/v) concentrations. In other comparative experiments the extent of suppression caused by CS was similar to that produced by 7,12-dimethylbenz[a]anthracene treatment.

The reason why known carcinogens, or indeed CS, suppress non-specific esterase activity, at present, remains unknown. But considering the results of previous experiments using the sebaceous gland test and despite the obvious drawbacks of the predictive value of such bio-assay systems, CS should be fully investigated for carcinogenic activity.

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Interaction of Hallucinogenic Drugs with Encephalitogenic Protein of Myelin

IMMUNOCHEMICAL techniques involving humoral antibody have long been used in elucidating the structural relationships of proteins and small antigenic molecules. Development of a quantitative technique for sensitized lymphocytes with high discriminatory capacity in respect to closely related antigens has made it possible to use these cells to assess structural requirements for antigenicity¹⁻³. When sensitized lymphocytes are brought into contact with specific antigen a material is liberated which lowers the electrophoretic mobility of normal guinea-pig macrophages. The change in cell mobility can be measured in a Zeiss cytopherometer. This assay has been used in the study of several experimental and human autoimmune diseases to give an accurate and quantitative assessment of the cellular immune response^{1,4}.

Lymphocytes from patients with multiple sclerosis and other degenerative neurological diseases have been shown to be sensitized to the encephalitogenic basic protein from human myelin (EF)⁵. Patients with malignant neoplasia also possess lymphocytes able to respond to EF and to a synthetic peptide Ser-Arg-Phe-Ser-Trp-Gly-Ala-Glu-Gly-Gln-Arg which corresponds to the main encephalitogenic determinant in the human protein⁶, that region of the protein which induces experimental autoimmune encephalomyelitis in guinea-pigs. Details of the method are given elsewhere³ and specimens are randomized and estimated blind.

Carnegie⁷ drew attention to the striking resemblance between the postulated structure for the encephalitogenic determinant and that required by a serotonergic receptor as calculated by Smythies, Benington and Morin⁸. However, the structure proposed by Carnegie did not completely agree with the structural requirements for encephalitogenicity set out by Westall *et al.*⁹. In particular in Carnegie's model glutamic acid was a key residue while Westall *et al.* thought this was unimportant. To resolve this conflict Smythies *et al.*^{10,11} proposed an alternative model where the above peptide was placed in an anti-parallel- β -pleated sheet conformation. Field *et al.*⁶ have demonstrated that serotonin can block the reaction between sensitized human lymphocytes and encephalitogenic protein (EF) or the above peptide provided it is added before the antigen. Serotonin had no effect in systems where the antigen was structurally unrelated to EF. Moreover, acetylcholine, succinylcholine, histamine, adrenaline, noradrenaline and (in the present study) dopamine were without effect.

We describe here the effect of indole derivatives related to serotonin on the interaction of human encephalitogenic protein with lymphocytes from patients with degenerative neurological disease. Some hallucinogenic drugs which are thought to react with serotonergic receptors in the central nervous system have also been studied.

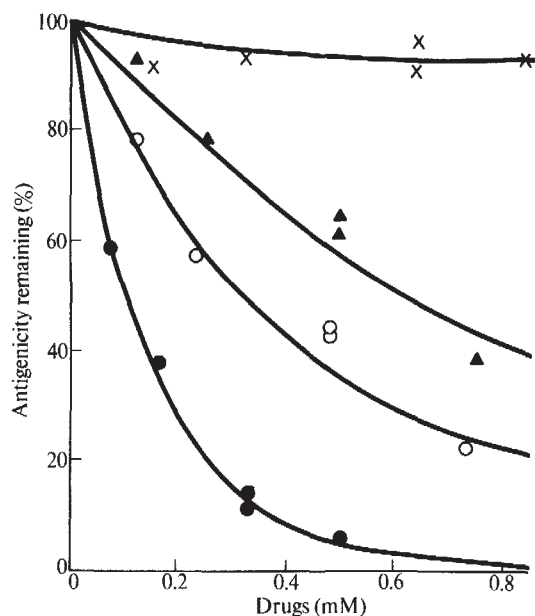


Fig. 1 Effect of indoles on the antigenicity of encephalitogenic protein of myelin. Antigenicity was determined in cytopherometer assay with lymphocytes from a patient with multiple sclerosis. Solutions of the drugs, 0.8 mg/ml., in tissue culture medium 199 were prepared, and 125, 250, 500 or 750 μ l. were mixed with 0.5×10^6 lymphocytes from a patient with multiple sclerosis and 10^7 guinea-pig macrophages in a total volume of 3 ml. medium 199. Encephalitogenic protein (EF, 100 μ g in 100 μ l.) was then added. The change in electrophoretic mobility of macrophages was then measured at 23° C after the customary incubation for 90 min. In the above system EF, in the absence of blocking agents, usually caused a decrease of around 0.25μ m s^{-1} V^{-1} cm^{-1} in the electrophoretic mobility of the macrophages. Results are expressed as relative mobility where the result with EF in the absence of any blocking agent is taken as 100%. Calculation³ showed that differences in mobility of 20% and 15% were significant at the 0.001 and 0.01 levels respectively. x, Tryptamine; ▲, 5-CH₃O-N,N-dimethyltryptamine; ○, 5-Cl-N,N-dimethyltryptamine; ●, 5-OH-tryptamine.

Lymphocytes, macrophages and encephalitogenic protein were prepared and used in the cytopherometer assay as previously described³.

Increasing concentrations of serotonin and drugs blocked the reaction between EF and lymphocytes (Fig. 1). All drugs showed no direct effect on the mobility of macrophages. The drugs are either reacting with the antigenic determinant on EF or with the complementary antibody-like molecule on the surface of specifically sensitized lymphocytes. Lymphocytes incubated with serotonin, washed and then used in the test react in exactly the same manner as do untreated cells indicating that serotonin is without effect on the lymphocytes. Also, the type of curve⁸ of Fig. 1 would not be produced if there was a direct effect on the cell. In preliminary experiments no significantly greater uptake of ¹⁴C-serotonin by reactive lymphocytes was observed. Thus we suggest that serotonin is interacting with EF. As the tryptophan region of EF interacts with the lymphocytes⁶ and as this region fulfils the structural requirements of a binding site for serotonin we assume that the loss of antigenicity results from the drug binding to this region of the protein. From a dose response curve for EF with lymphocytes¹² we estimated the amount of free EF required to elicit the particular response for all points on the curves (Fig. 1). The amount of bound EF was taken as the total EF (1.78 μ M) less the free EF taking the molecular weight of EF as 18,500¹³. In comparison the amount of bound drug was assumed to be negligible with the free drug concentration on a molar basis. From reciprocal plots of the drug concentration and the ratio of bound to total EF the apparent association constant K^1 was calculated from the slope of the regression line from the experimental points. Similar data were obtained for the binding of serotonin to a synthetic encephalitogenic peptide of only 9 amino-acids, Phe-Ser-Trp-Gly-Ala-Glu-Gly-Gln-Arg⁹. The

values of K for the association of serotonin to the peptide and EF were found to be 9.8×10^4 M^{-1} and 7×10^4 M^{-1} respectively. Similarly K^1 values for 5-chlorodimethyltryptamine and 5-methoxydimethyl-tryptamine were 4.3×10^4 M^{-1} and 2.9×10^4 M^{-1} . Because of the complexity of the assay system and the assumptions involved these values should be considered as approximate and confirmation by more rigorous techniques should be sought.

With the other drugs, tested at only one concentration (130 μ g ml^{-1}), we can estimate their relative ability to interact with EF by comparing the molar concentration of the drug with that of serotonin required to block the antigenicity of EF to the same extent (Table 1).

From the interaction of the hallucinogenic drugs with EF (Table 1) it is clear that apart from LSD they have less effect than serotonin. Tryptamine and simple indoles did not appear to interact with EF. The 5-methoxytryptamine derivatives are of interest because the 5-methoxy and dimethyl-5-methoxy derivatives had significant interaction but the bulkier diethyl and N-methyl-N-cyclopentanyl derivatives were without effect.

Table 1 Blocking by Indole Derivatives and Hallucinogenic Drugs of Antigenic Determinant of Encephalitogenic Protein in Reaction with Lymphocytes from Patients with Neurological Diseases

Compound	Relative antigenicity in presence of Patient A (stroke)	Relative antigenicity of drug Patient B (multiple sclerosis)	Relative molar ability to block antigenicity
None	100%	100%	
Significant blockage ($P < 0.001$)			
5-hydroxytryptamine (serotonin creatinine sulphate)*	12.5	12.4	1.0
N,N-dimethyltryptamine*	37.0	38.0	0.4
5-chloro-N,N-dimethyltryptamine HCl	—	43.0	0.6
D-lysergic acid diethylamide (LSD) D-tartrate	48.0	—	1.0
5-hydroxy-N,N-dimethyltryptamine (bufotenine)†	52.5	48.0	—
5-methoxy-N,N-dimethyltryptamine HCl	61.0	62.0	0.4
5-methoxytryptamine	63.5	65.0	0.3
3,4,5-trimethoxyphenethylamine HCl (mescaline)*	64.0	62.0	0.3
N,N-dimethyl-2,5-dimethoxy-4-methylamphetamine HCl (dimethyl DOM)	66.0	72.0	0.3
Insignificant blockage			
Tryptamine HCl*	92.0	—	0.0
Indole*	91.0	—	0.0
Hydroxyindole*	91.0	—	0.0
N-isopropyltryptamine maleate	102.0	—	0.0
Dehydrobufotenine HCl	98.0	—	0.0
5-methoxy-N,N-diethyltryptamine HCl	90.0	95.0	0.0
1-methyl-5-methoxy-N,N-dimethyltryptamine HCl	97.0	—	0.0
5-methoxy-N-methyl-N-cyclopentanyltrypamine†	98.0	—	0.0
5-benzyloxy-N,N-di-n-butyltryptamine HCl†	98.0	—	0.0
3-(β -N-piperidinoethyl) indole HCl	89.0	—	0.0
3-(β -N-pyrrolidinoethyl) indole HCl	93.0	—	0.0

All measurements were made in the cytopherometer assay with lymphocytes sensitized to encephalitogenic protein. In the incubation mixture 0.5×10^6 human lymphocytes were mixed with 10^7 guinea-pig peritoneal macrophages. The drugs, 400 μ g (except LSD 150 μ g), were added to the incubation mixture a few minutes before the addition of 100 μ g of the encephalitogenic protein and made to a total volume of 3.1 ml. with tissue culture medium 199.

Drugs marked † were not completely soluble in the incubation mixture.

Drugs marked * were from Sigma Limited. LSD was from Spofa United Pharmaceutical Works, Praha. Others were kindly given by Drs R. B. Barlow, F. Benington and R. D. Morin.

Moreover a methyl group at the 1 position blocked the ability of the indole to bind to EF.

Drugs known to be hallucinogenic are shown to partially block the reaction of the protein with lymphocytes (Table 1). Indole derivatives without hallucinogenic activity had no effect. LSD, mescaline and dimethyltryptamine¹⁴ are thought to interact with receptors for serotonin. However, correlation between hallucinogenic potency and blockade in this test is not complete. For example hallucinogenic potency runs d-LSD 5-methoxy-N,N-dimethyltryptamine N,N-dimethyltryptamine¹⁴ whereas the order for the last two is reversed in the current test. Moreover, N,N-dimethyl-2,5-dimethoxy-4-methylamphetamine (N,N-dimethyl-DOM), inactive as a hallucinogen¹⁴, shows some blocking activity. Therefore it appears that the receptors concerned must be similar but not identical.

The failure of tryptamine to block the antigenicity and the ability of serotonin to react suggests that charge-transfer reactions may be of prime importance. In addition, since 5-hydroxyindole was inactive the amine group is also important. From physical measurements EF appears to have an essentially random conformation in aqueous solution¹⁵, but in the presence of lipids changes to a mixture of α -helix and β -structure¹⁶. The anti parallel- β -pleated sheet conformation for the tryptophan region would provide a binding site which satisfies spatial requirements to accommodate the smaller hydroxytryptamine derivatives. Lymphocytes would be expected to recognize an ordered form of EF rather than a random structure and perhaps in our test system EF may associate with cell membranes and assume an ordered structure "recognized" by the drug and by the lymphocytes. Preliminary experiments in a purely aqueous medium have failed to show the same degree of association of (¹⁴C)-5-hydroxytryptamine for EF. Experiments with model membranes which incorporate EF may be necessary to confirm the binding we have demonstrated.

The association constant of $7 \times 10^4 \text{ M}^{-1}$ found for serotonin with EF is lower than that (10^7 M^{-1}) determined by Marchbanks¹⁷ for serotonin with nerve ending particles. There is evidence for the binding of serotonin by preparations of synaptosomal membranes^{18,19}. However, in Alivisatos *et al.*^{18,19} the equilibrium was displaced by tryptamine and hydroxyindole which do not interact with EF in our system and which are not hallucinogenic. Although the concentration of serotonin in brain is only 0.5 to 5 μM ²⁰, the local concentration, at least in cytoplasm of certain invertebrate cells²¹, can be as high as 4 mM. Thus, if serotonin were released in high concentration in close proximity to myelin protein significant interaction could occur.

Myelin fractions have been shown²² to contain between 12%²³ and 23%²² of the serotonin in brain²³. Alivisatos *et al.*¹⁸ has also demonstrated binding of ¹⁴C-serotonin to myelin. During rapid myelination in the rat between (7 and 14 days) there is a striking sigmoidal increase in the activity of associated enzymes²⁶. While tryptophan hydroxylase²⁵ activity, serotonin concentration²⁶ and myelin development showed a similar pattern with age during this critical period, the concentration of noradrenaline increased in a linear manner between birth and 42 days²⁶.

Monoamine oxidase binds serotonin prior to exerting its oxidative activity. This binding is blocked by pargyline (N-benzyl-N-methylpropynyl-amine HCl) which attaches to the active site of the enzyme²⁷, but is without effect on the antigenicity of EF. Thus the binding site on the oxidase for serotonin must be different from that on EF. Serotonin also interacts with the postsynaptic and presynaptic membranes in certain synapses. Imipramine is known to block the re-uptake of serotonin by presynaptic membranes²⁸ and also blocked the antigenicity of EF giving an association constant of approximately $6 \times 10^4 \text{ M}^{-1}$.

It is surprising that a myelin protein can interact with serotonin, as hallucinogenic drugs in general are usually assumed to influence serotonin receptors at synapses^{14,29,30}

though there is little direct evidence for this. Myelin is considered to be derived from and maintained by oligodendroglial cells which respond to serotonin in culture^{31,31} by changing their pulsation. Perhaps these cells have a more active role in the CNS and the drugs may be affecting their function.

As there is approximately 500–1,000-fold molar excess of EF compared to serotonin in the adult rat brain there cannot be one molecule of serotonin associated with each molecule of EF. A possible site for *in vivo* interaction is at the nodes of Ranvier in the central nervous system. Dickinson *et al.*³³ have suggested that the basic protein is localized in the intra period line of myelin which may be exposed, free of lipid, in this region. Alternatively from the imipramine result the encephalogenic determinant may merely be mimicking a synaptic receptor for serotonin which would have a similar structure. We can speculate that hallucinogenic drugs may exert their action along the course of the myelin sheath (perhaps in the vicinity of the nodes of Ranvier) rather than specifically at synapses. Indeed differential interference with conduction might lead to temporal dispersion of impulse volleys with consequent functional disturbance—both sensory and motor.

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Efficient Recognition of Pictures in Organic Amnesia

Weiskrantz and Warrington¹⁻⁵ have reported that, in patients with organic amnesia, considerable retention of new information may be demonstrated provided memory is prompted by "partial information" such as a fragmented form of a test picture or the first two letters of a test word. They contrast this evidence with the patients' very poor memory when recall or recognition is tested and propose that amnesia is a condition in which memories fail to undergo normal processes of decay or inhibition. According to this disinhibition hypothesis, testing with partial information constrains the number of alternatives between which the amnesic patient must choose and so evades the abnormal interference from irrelevant memories.

These authors have compared various methods of retrieval using words but not using non-verbal material. Other authors^{6,7} have shown relatively efficient recognition of pictures using multiple choice techniques but have not compared this technique with yes/no recognition. Multiple choice recognition constrains the alternatives between which the subject must choose. Hence, efficient recognition using this technique is consistent with the disinhibition hypothesis. No such constraints, however, are involved in yes/no recognition and, according to the theory, amnesics should be markedly impaired on such tests. In a preliminary study of two amnesic patients, we have compared the effects of these two techniques on picture recognition.

One patient (subject A) had an amnesic syndrome resulting from a vascular lesion and the other patient (subject B) had an amnesic syndrome associated with an encephalopathy. Both patients obtained above average IQs (WAIS) and were undemented apart from the amnesia. After intervals exceeding 1 min, neither patient could recall information such as names or pictures which he had been asked to remember, and usually failed to acknowledge that such a request had been made. In general, both were unable on request to describe any events in their lives during the past hour, day or week. No dysphasia was elicited.

Memory for pictures was tested by showing a series of full-page, coloured magazine pictures for 10 s each and later requesting yes/no recognition for half of them and two-choice recognition for the remainder. Subject A was shown fourteen pictures and, 10 min later, was again shown seven of these, one at a time, randomly interspersed with seven new pictures, and asked to state for each picture whether or not he had been shown it before. Immediately after this test, each of the remaining seven pictures originally shown was re-presented together with a new picture and the subject asked to point out the one he had been shown earlier. In the picture recognition test, subject A thus made fourteen yes/no responses and seven two-choice responses. Memory for pictures was examined in subject B using the same procedure as for subject A except that (i) he was initially shown twenty-four pictures to remember, (ii) he was tested after 20 min with twelve yes/no recognitions and six two-choice recognitions, (iii) he was tested on the remaining twelve pictures after 3.5 h with a further twelve yes/no recognitions and six two-choice recognitions. During the two shorter retention intervals both subjects were occupied with verbal tasks. The results are shown in Tables 1 and 2. *In toto* 93% of our subjects' recog-

Table 2 Two-Choice Recognition of Pictures

	Correct	Incorrect
Subject A (12-min retention)	6	1
Subject B (22-min retention)	6	0
(3.5-h retention)	6	0

Table 3 Yes/No Recognition of Words (Subject B)

	True positives	True negatives	False positives	False negatives
20-min retention	4	4	2	2

nition responses to pictures were correct and no false positive responses occurred.

In subject B, the 20-min retention, yes/no recognition experiment was replicated using single, common five-letter words instead of pictures. During the retention interval the subject was occupied with a non-verbal intelligence test. Results are shown in Table 3. Sixty-seven per cent of these responses were correct and half the errors were false positives. Because 50% correct is to be expected by chance, this result is not impressive and is consistent with Weiskrantz and Warrington's observation of poor word recognition in amnesics.

Two conclusions are suggested by these preliminary findings. (1) Yes/no recognition and two-choice recognition of pictures were both highly efficient over a period of 10 or 20 min and, in the one patient tested, over a period of 3.5 h. Our results therefore show that efficient recognition was possible without providing partial information or otherwise constraining alternative responses. (2) When a formally similar test procedure is employed, recognition of previously presented words is much less efficient than recognition of previously presented pictures. It is possible that this is no more than the exaggeration of a normal tendency⁸. Alternatively, amnesia may involve differential impairment of memory for different types of material.

Our results do not favour the suggestion that amnesic patients fail to remember appropriately through inability to inhibit competing memories. They do, however, suggest that the recognition performance of amnesic patients may be considerably affected by the material to be remembered. A theory of amnesia which neglects such differences may be difficult to sustain.

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Table 1 Yes/No Recognition of Pictures

	True positives	True negatives	False positives	False negatives
Subject A				
10-min retention	6	7	0	1
Subject B				
20-min retention	5	6	0	1
3.5-h retention	5	6	0	1

Protection against Experimental Allergic Encephalomyelitis

EXPERIMENTAL allergic encephalomyelitis (EAE) is an acute neurological autoimmune disease induced in laboratory animals such as guinea-pigs, rabbits, rats and monkeys by administration in complete Freund's adjuvant of a basic encephalitogenic protein (BE) isolated from the brain or spinal cord of

several animal species¹. We have recently shown² that the disease may be suppressed by intravenous injection of a synthetic amino-acid copolymer (denoted Cop 1). This copolymer is composed of alanine, glutamic acid, lysine and tyrosine, in a residue molar ratio of 6.0 : 1.9 : 4.7 : 1.0, and has an average molecular weight of 23,000. This basic polymer is not encephalitogenic² and is not a general non-specific immunosuppressive agent (our unpublished results). Whereas it efficiently suppresses the disease when administered after the basic encephalitogen, it cannot prevent the disease when injected intravenously in saline before the basic brain protein².

We now report that after successful suppression of the disease by Cop 1, guinea-pigs remain protected against subsequent injection of the basic encephalitogen in complete Freund's adjuvant. Moreover, the administration of a very small amount of the basic protein—much too low to provoke any clinical or histological symptoms—followed by three intravenous injections of an aqueous solution of Cop 1, efficiently protects the experimental animals from the disease.

It has been previously shown that animals which had recovered from EAE are subsequently resistant to the induction of the disease³⁻⁵. Our results suggest that for guinea-pigs in which EAE has been suppressed by injection of Cop 1, a very similar phenomenon occurs. Of fifty guinea-pigs challenged with 10 µg of BE in complete Freund's adjuvant (CFA) and treated with three intravenous injections of 1 mg each of Cop 1 at days 1, 6 and 11 after challenge, only fourteen guinea-pigs showed clinical symptoms of the disease. The surviving animals were divided into two groups which were rechallenged with 10 µg of BE 4 to 7 weeks following the last injection of Cop 1, respectively. None of the guinea-pigs in this experiment showed any clinical symptoms of EAE, and only three out of six showed any histological lesions in the brain. These changes in the brain were not due to the rechallenge with the BE, since in a control group of animals surviving EAE after treatment with Cop 1, and not rechallenged with BE, four out of six guinea-pigs showed similar mild histological lesions in the brain.

In this experiment, whereas protection against EAE was very efficient, the necessary initial exposure to a disease-inducing dose of BE still resulted in 28% of the animals becoming paralysed. This danger was subsequently avoided by using a low dose of BE for the initial exposure before the treatment with Cop 1.

The results (Table 1) show that, in contrast to a dose of 10 µg of BE, which induces the disease in 76% of the guinea-pigs, a dose of 0.1 µg of BE administered in complete Freund's adjuvant did not elicit any clinical symptoms of EAE nor any histological changes in the brains of fourteen animals tested. However, if this treatment with 0.1 µg of BE was followed by three intravenous injections of Cop 1 (1 mg each) 1, 6 and 11 days later, a subsequent challenge with 10 µg of BE in complete Freund's adjuvant induced the disease in only 14% of the animals. A control group receiving only Cop 1 under the same schedule before the challenge with BE did not show

any decrease in incidence of the disease as compared to the group deprived of any treatment except the challenge with the encephalitogen. Another control group treated only with 0.1 µg of BE before the challenge with the disease-inducing dose showed only limited protection against EAE. Pre-treatment with complete Freund's adjuvant alone did not give any protection either.

Attempts to protect against induction of EAE by treatment with Cop 1 following initial exposure to 10 µg or 100 µg of BE injected intravenously in saline proved unsuccessful. Only a delay in the onset of the disease was observed in these experiments, but there was no significant reduction in the number of animals showing clinical symptoms of EAE or histological changes in the brain. Thus, in the group receiving the pretreatment with intravenous injection of BE followed by three injections of Cop 1, twenty-six out of thirty-seven guinea-pigs (70%) were paralysed before the challenge with BE in Freund's adjuvant, as compared to thirty-two out of thirty-eight guinea-pigs (84%) showing paralysis after induction of the disease without previous treatment.

It seems, therefore, that effective protection against EAE by Cop 1 was achieved only following an initial injection of the BE under optimal immunization conditions in complete Freund's adjuvant. According to our recent findings (C. W., D. T., R. A., and M. S., unpublished work), there is an immunological cross-reaction at the cellular level between the basic encephalitogen and Cop 1. Our experiments might possibly be interpreted, therefore, in terms of triggering certain cells with the basic protein, and their subsequent tolerization or deviation of immune response, by Cop 1.

We have already mentioned that the few animals which recovered spontaneously from EAE are resistant to the induction of a second attack³⁻⁵. This is true also when most of the animals have survived following intravenous injections of a basic synthetic polypeptide. Several laboratories have reported that both suppression and prevention of EAE may be achieved by high doses of the basic encephalitogen itself or other neural proteins.

Thus, Kies and co-workers⁶⁻⁸ showed that intracutaneous injection of 2.5 ml. of encephalitogenic neural extracts in water-in-oil emulsion, given before the challenge, resulted in prevention of EAE. Similarly, Roboz-Einstein *et al.*⁹ reported that several neural proteins provided partial prevention against EAE when injected in high doses (8 × 100 µg) in incomplete Freund's adjuvant before the challenge with the disease-inducing dose of the encephalitogen. According to a more recent report, treating guinea-pigs with BE in incomplete adjuvant before encephalitogenic challenge suppresses development of both EAE and delayed hypersensitivity and simultaneously evokes anti-BE antibodies¹⁰. Moreover, the 2-hydroxy-5-nitrobenzyl bromide (HNB) derivative of BE (in which the single tryptophan residue is blocked) was also found effective in prevention of EAE in both guinea-pigs¹¹ and rhesus monkeys¹². In all these reports the amount of the encephalitogen or its derivative used for prevention was very high

Table 1 Protection against EAE

Treatment	Clinical disease		Histological changes		Degree
	Incidence*	<i>p</i> †	Incidence*	<i>p</i> †	
10 µg BE in CFA (control)	32/42 (76%)		22/24 (96%)		++, +++
0.1 µg BE in CFA	0/14	<0.001	0/14	<0.001	
0.1 µg BE, at day 21 challenge with 10 µg BE	15/35 (43%)	<0.05	17/24 (71%)	<0.25	+, ++
0.1 µg BE followed by three injections of 1 mg Cop 1 at days 1, 6, 11 and at day 21 challenge with 10 µg BE	5/35 (14%)	<0.001	13/26 (50%)	<0.005	+, ++
Three injections of 1 mg Cop 1 at days 1, 6, 11 and at day 21 challenge with 10 µg BE	10/12 (83%)	<0.8	11/12 (92%)	>0.9	++, +++
CFA alone, at day 21 challenge with 10 µg BE	11/15 (73%)	<0.7	14/15 (93%)	>0.9	++

* Each incidence figure gives the cumulative results of three–six individual experiments.

† Standard deviations were calculated and *t* tests performed. The *P* values represent the statistical significance of differences from the control group.

compared to the encephalitogenic dose of the protein. According to Anderson *et al.*¹³, there are conflicting results and similar treatments may in some systems induce EAE.

Our results demonstrate that even minute amounts of BE, far too low to induce clinical effects, injected in complete adjuvant before the encephalitogenic dose have a limited protection against EAE. However, this protection is highly potentiated if this initial injection is followed by three consecutive injections of a basic synthetic polypeptide. The prevention procedure consists, therefore, of two stages, neither of which involves any encephalitogenic exposure or general immunosuppressive activity. Nevertheless, it protects the animals efficiently from high doses of the encephalitogenic protein, which would have otherwise induced the disease in most animals.

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Additional Mitosis in Wheat Pollen induced by Ethrel

ETHREL (2-chlorethylphosphonic acid) can induce male sterility in several crop plant species including cucumber¹ and wheat². This effect would have considerable economic significance if it could be used for inducing male sterile seed parents for production of F₁ hybrid crop varieties. The use of Ethrel in breeding hybrid varieties cannot be assessed until the basis of its action in causing abnormal anther development is understood. Consequently we have investigated the extent and the time of induction and appearance of these abnormalities.

We found that the critical deviations occur late in pollen development and often involve the induction of additional nuclear divisions in pollen grains. These effects appeared only in anthers treated with Ethrel some time before meiosis had been initiated. These observations are additionally significant because the production of haploid sporophytes from plant anthers depends upon the continuance in pollen grains of nuclear divisions, and these apparently can be stimulated by

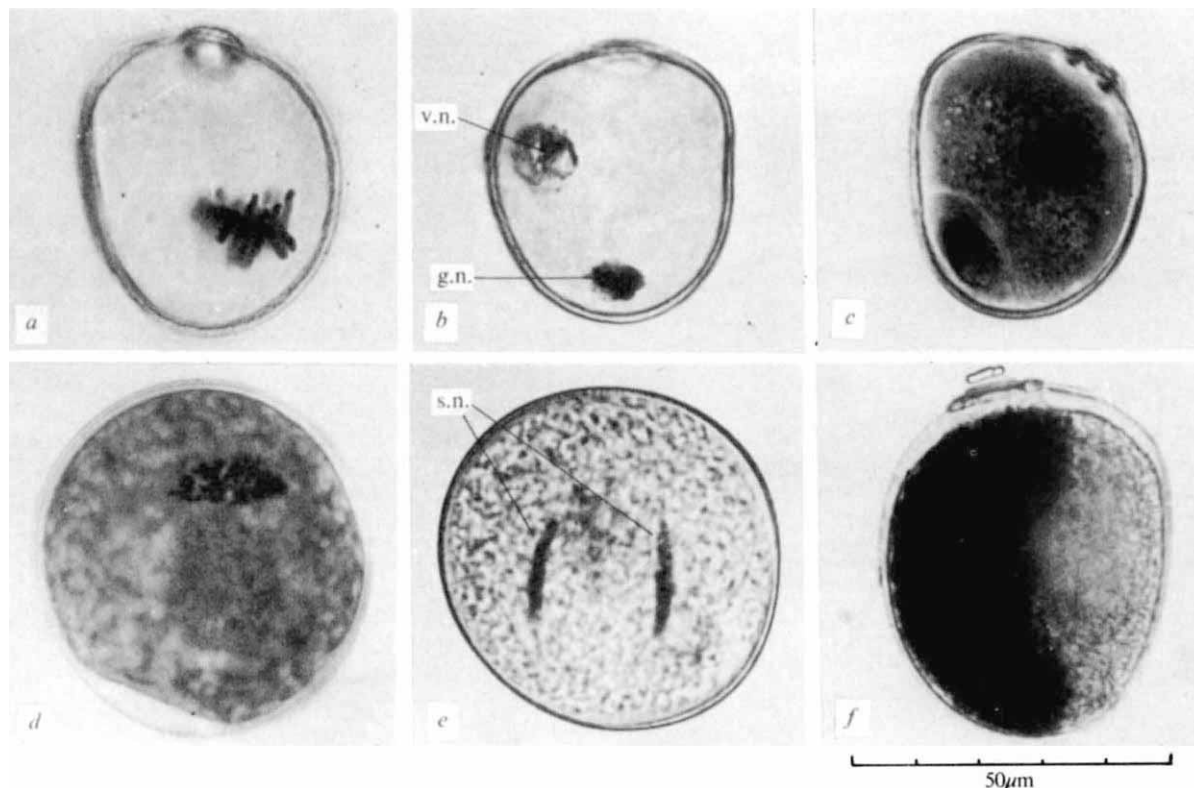


Fig. 1 Stages in normal pollen development of Chinese Spring wheat. Pollen grains are shown at (a) metaphase of first pollen grain mitosis, (b) soon after first pollen grain mitosis, (c) mid-way between first and second pollen grain mitoses, (d) metaphase of second pollen grain mitosis, (e) mid-way between second pollen grain mitosis and dehiscence, and (f) at dehiscence. After first pollen grain mitosis one nucleus becomes large and diffuse (the vegetative nucleus, v.n.) while the other becomes small and dense (the generative nucleus, g.n.) (b and c). Division of the generative nucleus at second pollen grain mitosis produces two nuclei (sperm nuclei, s.n.) which become greatly elongated (e). Starch grains first appear after first pollen grain mitosis (c) and persist until the time of dehiscence when they start to be degraded. Pollen grains stained for starch at dehiscence show localized asymmetrical staining (f).

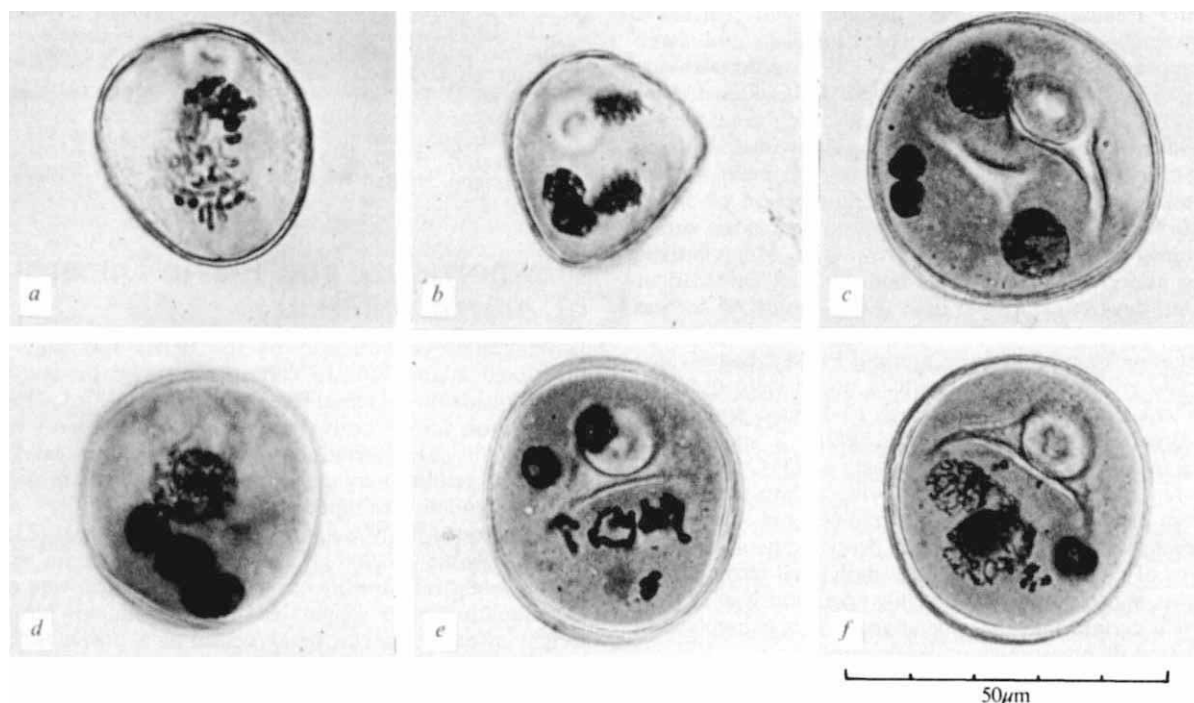


Fig. 2 Abnormal pollen development in Ethrel treated Chinese Spring anthers. At abnormal second pollen grain mitosis both nuclei divide either synchronously (a), or asynchronously (b). Tetranucleate pollen grains produced by abnormal second pollen grain mitosis contain variable numbers of large diffuse (vegetative type) and small dense (generative type) nuclei (c and d). Abnormal second pollen grain mitoses occur in starch free almost non-vacuolated grains (e and f) and none of the nuclei produced elongate to appear like sperm nuclei (e and f).

Ethrel. Ethrel and similar substances may be useful in increasing the availability of haploids grown from pollen grains.

We sprayed groups of three replicate *Triticum aestivum* var. Sirius plants with about 20 ml. of seven aqueous Ethrel solutions whose concentrations ranged from 250–8,000 p.p.m. No wetting agent was used. Plants were treated when their leading tillers were 42, 35, 28, 21, 16 and 13 days prior to anthesis. Male sterility, measured by grains per spikelet, was induced only by Ethrel concentrations of 2,000 p.p.m. or more, applied at the last three times (Table 1).

In florets with induced male sterility, anther development was abnormal. Anthers were often reduced in size and extrusion and dehiscence frequently failed. Alternatively, extrusion was reduced compared with untreated anthers and dehiscence either failed or released sterile pollen.

Spikelets from plants sprayed with 4,000, 6,000 and 8,000 p.p.m. Ethrel were fixed at intervals after the treatment in 1 : 3 acetic alcohol and anthers from treated florets were squashed in acetocarmine for light microscopy. Serial examination of slides showed that development was normal during meiosis and early pollen development until first pollen grain mitosis (PGM 1), even though the concentration of Ethrel was sufficient to induce male sterility. Pollen was examined from dehiscent and undehiscent anthers with abnormally short filaments after extrusion. In both instances the pollen grains were mostly of normal size and external appearance, that is they had a well formed wall and a single prominent germination pore. They differed from normal pollen at dehiscence, however, by containing few or no starch granules, no elongated sperm nuclei, and, occasionally, more than three nuclei.

The durations were determined^{3,4} of premeiotic interphase (48 h), meiosis (24 h) and pollen maturation (7.5 days) in *T. aestivum* var. Chinese Spring wheat grown at 20° C with continuous light. The first and second pollen grain mitoses occur 2.5 and 5.0 days after the completion of meiosis. Ethrel experiments were, therefore, repeated using Chinese Spring grown under controlled conditions in an attempt to discover, first, the critical period at which anthers must be treated with Ethrel if sterility is to be induced, and second, the stage of development at which pollen first appears abnormal.

Table 1 Mean Seed Set per Spikelet in Ethrel Treated Plants

Time of application (days before anthesis)	Concentration (p.p.m.) of Ethrel				
	0 (control)	2,000	4,000	6,000	8,000
21	1.46 (282)	0.13 (173)	0.01 (190)	0.00 (73)	0.00 (71)
16	1.34 (339)	0.85 (168)	0.39 (289)	0.87 (217)	0.38 (272)
13	1.88 (295)	1.02 (127)	0.54 (231)	0.12 (310)	0.39 (297)

Number of spikelets scored given in parentheses.

Chinese Spring plants were allowed to equilibrate in the controlled environment for five days and were then sprayed with 20 ml. of solution containing 8,000 p.p.m. Ethrel. No wetting agent was used. Immediately prior to spraying, the developmental stage of individual tillers was estimated, either from the appearance of the flag and boot leaves or from the cytology of fixed and stained anthers from individual spikelets sampled through a small vertical slit in the leaf sheaths surrounding the spike. Tillers or florets were sampled at daily intervals after spraying, and were fixed for cytological examination.

Anthers from heads estimated to be at or after meiosis at the time of Ethrel treatment completed normal pollen development and anthers dehiscence at the expected time. Anthers from heads estimated to be from one to five days premeiosis at the time of Ethrel treatment exhibited normal meiosis and early pollen development up to and including PGM 1. Abnormal development first appeared just before second pollen grain mitosis (PGM 2).

In normal pollen development (Fig. 1 a–f), the products of PGM 1 differentiate into a diffuse vegetative nucleus, which does not divide again, and a smaller generative nucleus which comes to lie at the opposite end of the grain from the germination pore and the vegetative nucleus. At PGM 2 only the generative nucleus divides and the two sperm nuclei produced subsequently become greatly elongated (Fig. 1e). Soon after PGM 1 starch granules appear, then increase in size and number until by PGM 2 they pack the pollen grain, making observation of the division extremely difficult. Starch granules persist until dehiscence, at which time the pollen grain is trinucleate.

In Ethrel treated anthers the vegetative and generative nuclear products of PGM 1 differentiated normally and starch granules appeared. About 24 h before PGM 2 would normally occur, however, the starch granules began to be degraded, so that by PGM 2 the two nuclei were clearly seen in an almost non-vacuolated cytoplasm. Later both nuclei divided, in many cases synchronously, and at about the time after meiosis when PGM 2 would normally be expected. Examination of pollen grains with more than three nuclei showed that none subsequently elongated to the shape of sperm nuclei. Many anthers containing abnormal pollen grains had still not extruded or dehiscent ten days after normal time. Examination of anthers sampled at or after the normal dehiscence time showed that many of the nuclei produced at abnormal PGM 2 had divided again. Pollen grains containing up to 8 nuclei were observed in anthers which had undergone meiosis 10–12 days previously. Anthers already containing abnormal PGM 2 stages were transferred to culture on supplemented agar at 23°C for several days. A few yielded pollen grains with up to 15 nuclei. Nuclei from abnormal PGM 2 were of two types; large and diffuse (vegetative type), or smaller and denser (generative type). The number of each varied from 0–4 in individual tetranucleate pollen grains. When both nuclei divide synchronously at PGM 2 (Fig. 2a) it is certain that the vegetative nucleus is involved in the production of supernumerary nuclei.

At the Ethrel concentration used there is a critical period when the chemical must be applied if it is to induce male sterility. This period ends at about the time meiosis is initiated in pollen mother cells and includes the premeiotic interphase. It is highly significant that while the target period for induced male sterility is apparently premeiotic, no effect of the chemical on archesporial development is seen before about 5–6 days later, and that Ethrel applied just before the stage when abnormal development may first appear has no effect on pollen development. Other work in this laboratory has recently indicated the existence of sensitive premeiotic stages in wheat at which chromosome pairing during meiosis and pollen pore formation after meiosis can be affected^{5,6}. Ethrel is known to break down in plant cells at pHs below 4.0 releasing ethylene, a molecule now widely acknowledged as having hormonal properties in plants^{7,8}. Hormones are thought to act sometimes by directly affecting gene transcription. A possible explanation of the effect of Ethrel is therefore that it alters the production of long-lived messenger RNA transcribed before meiosis but necessary for normal pollen development several days later.

Haploid plants have been produced from pollen in tobacco^{9,10}. Two barriers block the successful repetition of haploid plant production from pollen in wheat and many other species. For haploid sporophytes to occur, the pollen must be switched from the normal gametophyte pattern of development and mitotic divisions must be induced in pollen nuclei. Once initiated, mitotic activity must be sustained and cell walls formed to enclose its products. The products of abnormal PGM 2 (Fig. 2) are very similar to the early stages of haploid production from pollen in tobacco. The first barrier to the production of haploid sporophytes appears therefore to be removed in Ethrel treated wheat anthers. Experiments to culture the products of abnormal PGM 2 have already shown that further division cycles can be achieved. It seems reasonable to anticipate that further attempts to culture anthers from Ethrel treated plants may lead to the production of haploids in wheat and possibly in other species.

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Newborn Size and Pelvic Dimensions of *Australopithecus*

IN mammals construction of the pelvis not only reflects functional adaptations to certain modes of locomotion but also depends on maternal-foetal size relationships. Therefore, information about body weight and head size of newborn *Australopithecus* in relation to the size of the female pelvic inlet is of evolutionary significance with respect to the adaptation of hominids to bipedalism.

Estimates of body weight for adult *A. africanus* (22,500 g)¹ and *A. robustus* (50,000 g)² combined with data on maternal-foetal weight relationships in living primates provide a means of estimating birth weights for these hominids. Since the weight of an organ can be expressed as a power function of the body weight, it is assumed that in primates maternal and foetal (birth) weight are in allometric relationship. Foetal weight (F) is given in terms of the initial size constant (b) and the maternal weight (M) raised to an exponent α (constant of allometry). Thus $F = b \cdot M^\alpha$, or $\log F = \log b + \alpha \cdot \log M$. This is tested by plotting $\log F$ against $\log M$ for fifteen extant species of simian primates, based on published^{3–5} data (Fig. 1). The least squares equation is $\log F = 0.70 \cdot \log M$, or $F = M^{0.70}$. The initial size constant is $\log b = 0$, or $b = 1$. The correlation coefficient is 0.98.

From this equation the mean value of $\log F$ for any given $\log M$ can be predicted. Observed mean maternal weights, observed and expected mean foetal weights for pongids and hominids are given in Table 1. It is interesting that whereas expected values of foetal weights in *Pongo pygmaeus* and *Pan troglodytes* are almost identical to the observed values, in *Gorilla gorilla* the expected value overestimates the observed value, and in *Homo sapiens* the expected value underestimates

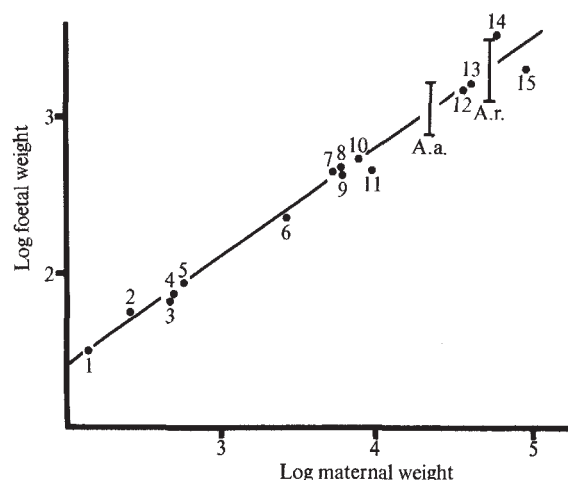


Fig. 1 Maternal-foetal weight relationships in fifteen extant species of simian primates, and 95% confidence intervals of expected mean foetal weights for *Australopithecus africanus* (A.a.) and *Australopithecus robustus* (A.r.). The log of the maternal weight is plotted against the log of the foetal weight. The least regression is drawn. Numerical designation of species: 1, *Cebuella pygmaea*; 2, *Callithrix jacchus*; 3, *Saguinus tamarinus*; 4, *Saguinus oedipus*; 5, *Saimiri sciureus*; 6, *Cebus capucinus*; 7, *Lagothrix lagothricha*; 8, *Alouatta palliata*; 9, *Macaca mulatta*; 10, *Ateles geoffroyi*; 11, *Nasalis larvatus*; 12, *Pongo pygmaeus abelii*; 13, *Pan troglodytes*; 14, *Homo sapiens*; 15, *Gorilla gorilla*.

the observed value. For *A. africanus* the estimated mean foetal weight equals 1,120 g with a 95% confidence interval from 760 to 1,660 g. For *A. robustus* the estimated mean foetal weight equals 1,950 g with an interval from 1,230 to 3,090 g.

It is obvious that with respect to birth weight *Homo sapiens* has a unique position among living primates. How can this trend toward increased birth weight be interpreted with respect to hominid evolution? Increase in birth weight during hominid evolution must have occurred in one of two ways: (1) either as a step-like displacement of regressions of foetal weight on maternal weight, or (2) as a single allometric shift in the relationship between foetal and maternal weight.

With regard to brain-body size relationship in hominids, Kinzey⁶ suggested that the increase in hominid cranial capacity during the Pleistocene has to be viewed as the result of a single positive allometric shift in the relationship between brain size and body size. *A. africanus* was involved in this shift, but not *A. robustus*. Assuming that a similar trend, based on a single allometric shift, has affected the maternal-foetal weight relationship in *A. africanus*, the following inferences can be made. Birth weight of *A. africanus* would have to be estimated to be in the upper half of the expected range, between 1,120 and 1,660 g, and probably closer to the upper limit. Taking for example the exact upper limit (1,660 g) the hominid regression line constituted by *A. africanus* and *Homo sapiens* would be perfectly parallel to the primate regression line, maintaining the same constant of allometry (0.70), but differing from the latter by an initial size constant value of 1.47. A birth weight estimate for *A. africanus* higher than 1,660 g can be ruled out, since this would imply that in the hominid regression the constant of allometry would be lower than in the primate regression. Even with this maximum possible estimate of birth weight, newborn *A. africanus* would still have been quite small, only slightly larger than average newborn chimpanzees.

On the other hand, if the increase in birth weight during hominid evolution followed a pattern of steplike displacements of regressions of foetal weight on maternal weight, birth weight estimations for *A. africanus* have to be markedly lower than the observed average weight of newborn orangutans.

The size of newborn *A. africanus* becomes of evolutionary significance when studying its relationship to the dimensions of the female pelvic canal. Successful parturition in mammals depends chiefly on the relationship between the principal diameters of the head of the foetus at term and those of the female pelvic inlet.

Dimensions of the pelvic inlet of *A. africanus* (STS 14), which represents a mature, possibly female individual¹, are 99 mm (transversal diameter) and 85 mm (sagittal diameter). The head size of newborn *A. africanus* can be estimated as follows. Newborn cranial capacity in relation to birth weight is quite constant among great apes and modern man. In chimpanzees relative cranial capacity of newborns averages 9.7%^{7,8}. In modern man the corresponding figure is 9.9%⁷.

Based on a relative cranial capacity of 9.8% and a birth weight estimate of 1,120 g, newborn cranial capacity in *A. africanus* would be 110 cm³. Based on the maximum birth weight estimate (1,660 g) the corresponding cranial capacity would be 163 cm³. The reasonableness of these figures can be tested by comparing them with the average cranial capacity of adult *A. africanus*, which has been calculated to be 442 cm^{3,9}. Newborn *A. africanus* would thus have reached between 24.9 and 36.9% of the adult cranial capacity which compares excellently with the values for modern man (23.3%)¹⁰ and chimpanzee (40.5%)⁷.

Comparing the possible range of cranial capacity in newborn *A. africanus* (110–163 cm³) with the actual range in newborn chimpanzees (139–171 cm³; mean 155 cm³)^{7,8} it can be inferred that the principal dimensions of the head would have been very similar in these two forms. Mean head diameters for newborn chimpanzees are 83 mm (head length) and 71 mm (head breadth)¹¹. Since head dimensions of newborn *A. africanus* would have been only slightly different from those of newborn chimpanzees, they would definitely have been smaller than the principal diameters of the pelvic inlet of STS 14. Even a newborn *A. africanus* with a head the size of a newborn gorilla could have passed through the pelvic inlet of STS 14.

The conclusion that newborns of *A. africanus* were quite small in relation to the female pelvic inlet suggests that (1) delivery in *A. africanus* was quick and easy which could have been a large selective advantage, and that (2) in the early stages of hominid evolution selective pressures for enlarging the pelvic canal to ensure parturition may have been minor or even absent; selective forces toward highly efficient construction of the pelvis for bipedalism could have been stronger, which would support the hypothesis that *A. africanus* was at least as well¹ if not better¹² adapted to bipedal locomotion than modern man.

I thank Dr J. T. Robinson for data on the pelvic dimensions of STS 14 and Dr W. G. Kinzey for helpful comments. Mrs J. Noda prepared the figure.

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Table 1 Maternal-Foetal Weight Relationships in Pongids and Hominids

Species	Observed mean maternal weights		Observed mean foetal weights		Expected mean foetal weights	
	(g)	(log)	(g)	(log)	(g)	(log)
<i>Pongo pygmaeus</i>	37,000	4.56	1,500	3.17	1,550	3.19 ± 0.18 *
<i>Pan troglodytes</i>	40,600	4.60	1,600	3.20	1,660	3.22 ± 0.19
<i>Gorilla gorilla</i>	90,000	4.95	2,000	3.30	2,890	3.46 ± 0.23
<i>Homo sapiens</i>	60,000	4.77	3,300	3.51	2,200	3.34 ± 0.21
<i>Australopithecus africanus</i>	22,500 †	4.36			1,120	3.05 ± 0.17
<i>Australopithecus robustus</i>	50,000 †	4.70			1,950	3.29 ± 0.20

* 95% confidence limits.

† Estimates.

Use of Waste Materials for Revegetation of Chromate Smelter Waste

ALTHOUGH chromate smelting is of world-wide application, there is no reported information on the correction of substrate toxicity in residues from the industry. This has prompted Lancashire County Council to conduct investigations into techniques of revegetation of the waste in order to reclaim the derelict site of one of Britain's three principal smelters, two

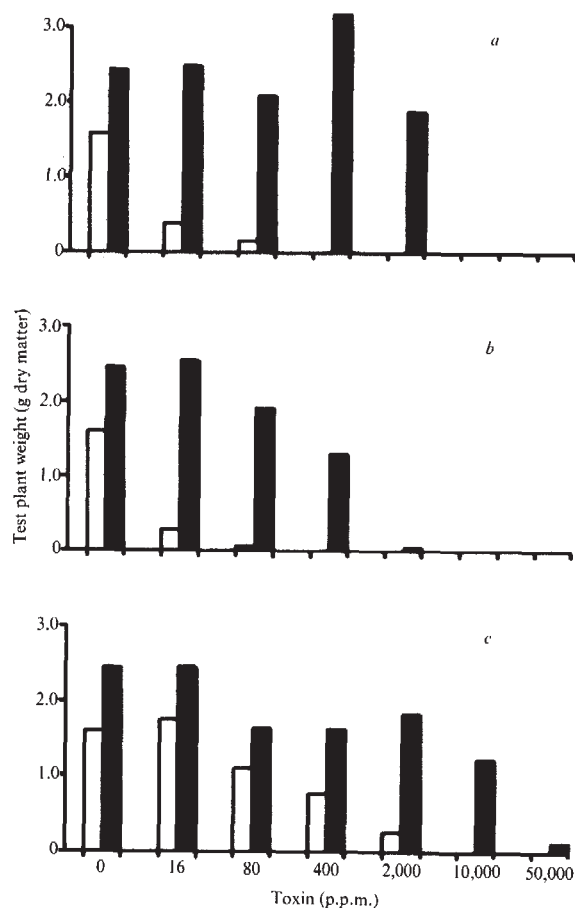


Fig. 1 Effect of peat on toxicity caused by chromates and unweathered waste. *a*, Sodium chromate, $\text{Na}_2\text{CrO}_4 \cdot 10\text{H}_2\text{O}$; *b*, sodium dichromate, $\text{Na}_2\text{Cr}_2\text{O}_7 \cdot 2\text{H}_2\text{O}$; *c*, unweathered waste. □, Sand only as diluent; ■, sand plus 20% peat as diluent. Growth nil where histograms not shown.

of which have now ceased production. The chief conclusions of this work are that the waste can be revegetated for amenity grassland by treatment with two other wastes.

Chromates were extracted from chromite by smelting with soda ash and lime. The waste is intensely phytotoxic, 200 p.p.m. in sand inhibiting plant growth by 50%. Toxicity is primarily due to calcium chromate (mean 46 milliequivalents/kg soil chromate ± 45 s.d.) but the presence of calcium hydroxide causes high pH (9.6 ± 1.2 s.d.) and greatly increased toxicity. Thus, although pH correction will decrease toxicity, reduction in chromate concentration is necessary for satisfactory vegetation establishment.

Experiments with amendment materials have shown that dilution with sand or soil is ineffective as a means of eliminating toxicity (my unpublished work; V. Breeze and A. D. Bradshaw, personal communication). Previous methods of correcting metal toxicity in smelter wastes have involved the use of organic materials¹⁻³ because toxic metal cations form stable complexes with organic matter^{4,5}. Because toxicity in the present situation is anionic, it was considered unlikely that organic matter would be effective unless chromate could be converted to the cationic state. Chemical reduction with ferrous sulphate residues from the titanium extractive industry was considered to be a feasible method of achieving this as well as correcting the high pH situation.

Waste containing 50 mEq/kg water soluble chromate and of pH 12.0 was diluted with granulated sedge peat as an organic matter source, soil and sand being used as control diluents. The effect of ferrous sulphate ($\text{FeSO}_4 \cdot 4\text{H}_2\text{O}$) was investigated on all media at a rate equivalent to 2,500 kg/hectare. Table 1 shows that peat is far superior to sand or soil in reducing toxicity and that ferrous sulphate reduces toxicity in all media.

Thus, chemical reduction is not necessary for organic matter to be effective, and ferrous sulphate will itself alleviate toxicity provided that the waste is sufficiently diluted.

The efficiency of organic matter in reducing chromate toxicity is confirmed by the data presented in Fig. 1, the effect being independent of the form of chromate. Presumably the level of plant-available chromate is reduced by an ion-association process. The superiority of peat in the first experiment was reflected in the levels of ammonium acetate extractable chromate in the 10% waste mixtures. These were 8.2 mEq/kg in soil and only 0.9 mEq/kg in peat.

To compare the importance of ferrous sulphate as a chemical reducing agent and as a substrate acidifier, various concentrations of waste in sand were treated at rates up to 25,000 kg/hectare $\text{FeSO}_4 \cdot 2\text{H}_2\text{O}$. Control substrates with high chromate (25 mEq/kg) but nil hydroxide, and low chromate but high hydroxide (500 mEq/kg), were similarly amended. Table 2 shows that reduction of toxicity may be attributed to chromate reduction and/or pH effects depending on the chemical status of the substrate. But chromate reduction is of principal importance in most cases. Further, in waste diluted 20 times or less, ferrous sulphate will not eliminate toxicity completely so the substrate should be initially amended with peat or sewage sludge from the activated sludge process.

Alleviation of toxicity by ferrous iron is presumably due to trivalent cationic chromium being less toxic than chromate

Table 1 Mean Shoot Dry Matter of *Lolium perenne* grown in Substrates contaminated with Unweathered Chromium Waste

Diluent	Treatment	Waste (%)			
		Nil	2.5%	5%	10%
Sand	Nil	17.3 $\pm$ 4.0	0	0	0
	FeSO_4	15.7 $\pm$ 5.1	1.6 $\pm$ 0.4	0*	0*
Soil	Nil	23.4 $\pm$ 5.6	3.5 $\pm$ 1.6	0*	0
	FeSO_4	22.2 $\pm$ 3.9	11.9 $\pm$ 1.1	0.7 $\pm$ 0.4	0*
Peat	Nil	14.6 $\pm$ 1.4	13.8 $\pm$ 2.3	13.5 $\pm$ 2.3	8.8 $\pm$ 0.5
	FeSO_4	7.0 $\pm$ 0.5	14.9 $\pm$ 3.2	13.1 $\pm$ 1.7	11.5 $\pm$ 2.8

* Germination but severely stunted roots and no significant dry matter production.

Mean values in grams $\pm$ s.d. are from 4 replicates.

Table 2 Effect of Ferrous Sulphate on Toxicity and pH of Substrates high in Chromate and/or pH

Tonnes/hectare $\text{FeSO}_4 \cdot 2\text{H}_2\text{O}$	Dry weight (g)		pH
	D.W. 20% waste	D.W. 10% waste	
0	0	0	9.6
5	0	0	9.1
10	0	0	8.8
15	0	0	8.4
20	0	0.01	8.3
25	0	0.01	8.1
5% waste			
0	0	0.59	9.0
5	0	1.40	8.1
10	0	2.19	7.8
15	0.02	2.33	7.5
20	0.16	2.16	7.3
25	0.45	2.37	7.3
0.1% waste			
0	2.40	2.96	7.6
5	2.57	3.29	7.6
10	2.68	3.14	7.5
15	2.70	2.98	7.5
20	2.55	3.33	7.5
25	2.86	2.83	6.9
Control (high Cr)			
0	0	0.10	12.4
5	0	0.15	11.8
10	0.16	0.30	11.7
15	0.08	0.38	11.4
20	1.41	0.39	10.5
25	1.47	0.47	9.8
Control (high pH)			

Values are means of 2 replicates.

under the conditions existing in the substrate. Robinson *et al.*⁶ state that chromates are more toxic than chromium salts, but the differences must be considerable to explain the present findings. This was confirmed in a further experiment; 2.4 p.p.m. chromium as chromate inhibited growth of white mustard by 80% in sand whereas 2,000 p.p.m. chromium as chromic sulphate reduced growth by only 20%, probably because of chromium precipitation as the hydroxide.

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Relationship between the Concentration of Caesium-137 in Milk and Man

CAESIUM-137, which is present in the fallout from nuclear explosions and is a potential hazard to man, is detectable in most components of the diet, but the chief sources are milk and dairy produce^{1,2}. Models that predict levels of caesium-137 in the food chain and in man have been proposed³, but they are restricted to a given geographical region. Because of diversity in dietary habits and food origins, we have attempted to relate the concentration of caesium-137 in man to its concentration in milk. This procedure should be satisfactory for extrapolation to the rest of the diet provided the variation of the concentration of caesium-137 in milk with time approximately parallels analogous variations in the remainder of the diet.

Retention of ¹³⁷Cs in man can be described by a two-exponential function^{4,5}; a small fraction (~0.1) has a half-life of 1 or 2 days, and the remainder has a half-life of 100–200 days. In models predicting long-term retention, the short-lived component is not significant, except that it reduces slightly the effective intake.

Concentrations of ¹³⁷Cs in milk in the United Kingdom are published as mean quarter-year values⁶. We have taken these values to be true for the middle of the quarter, and have calculated the concentration at other times by linear interpolation. Thus, if m_{i-1}, m_i are the published values for successive quarters the concentration at an intermediate time, τ , will be given by:

$$m(\tau) = m_{i-1} + \frac{(m_i - m_{i-1}) \times \tau}{\Delta t}$$

where $\Delta t = \frac{1}{4}$ year. Assuming that the dietary intake rate of ¹³⁷Cs is proportional to its concentration in milk, and adopting a single compartment model, the concentration in the body, c , is found by solving the equation $dc/dt = k m - \lambda c$ where k is a constant of proportionality which expresses the amount of caesium absorbed as an equivalent volume of milk and λ is the retention constant of the compartment. The solution has the form:

$$c_i = c_{i-1} e^{-\lambda \Delta t} + k \int_0^{\Delta t} m(\tau) e^{-\lambda(\Delta t - \tau)} d\tau$$

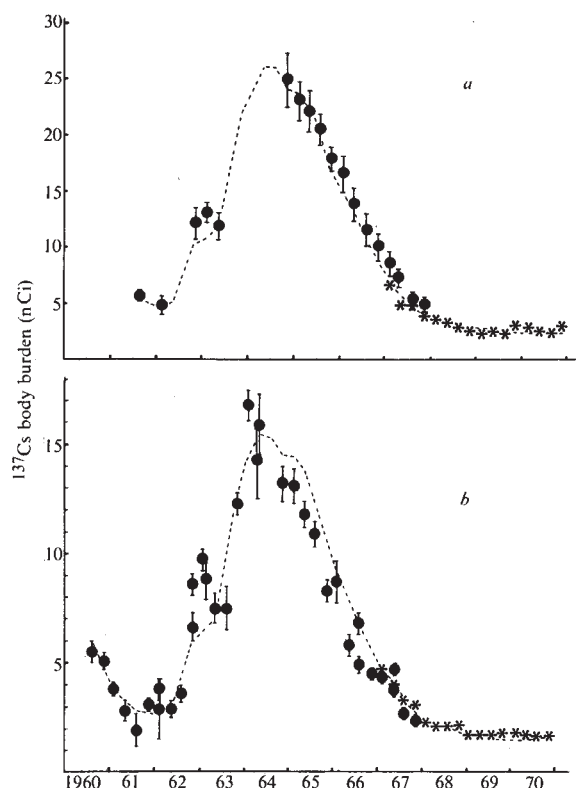


Fig. 1 Concentration of ¹³⁷Cs in man. The broken line shows the calculated curve for the best fit to observed mean values, (a) for the male population, and (b) for the female population. ●, Results from Godfrey and Vennart⁸; *, results from D. H. M. and L. B.

where c_{i-1}, c_i are successive mid-quarterly values of the concentration of caesium-137 in the body.

Measured body levels of ¹³⁷Cs in men and women for the period 1967–1970 are given in Tables 1a and 1b. These values, grouped to give quarter-year averages, were obtained from more than one thousand assays with the Leeds whole-body counter⁷. Healthy volunteers, and hospital patients referred to the unit for whole-body potassium measurements, were used, and we combined results with others published for an earlier period⁸.

Best estimates for values of the parameters in the model, the decay constant and the dietary intake rate, were obtained by a computer-based weighted least-squares method. Data for males and females were fitted separately and are shown, with the fitted function, in Fig. 1. Half-life values of 138 and 161 days were found for the male and female populations respectively. Corresponding values for the rate of intake were

Table 1a Concentration of ¹³⁷Cs in Males. Mean Values for Quarter-Year Periods (with s.e.)

Year	No.	Total nCi	pCi/kg body wt.	pCi/g potassium
1967 (1)	25	6.56 ± 0.47	98.2 ± 5.3	54.1 ± 2.7
(2)	19	4.68 ± 0.40	72.6 ± 4.7	40.7 ± 2.7
(3)	33	4.78 ± 0.45	73.8 ± 6.3	42.3 ± 3.2
(4)	52	3.77 ± 0.23	56.5 ± 2.8	28.9 ± 1.5
1968 (1)	61	3.48 ± 0.16	50.1 ± 2.2	25.4 ± 1.0
(2)	83	3.34 ± 0.18	46.5 ± 2.3	25.4 ± 1.5
(3)	42	2.84 ± 0.14	39.6 ± 1.8	22.3 ± 0.9
(4)	39	2.73 ± 0.15	39.9 ± 2.6	22.2 ± 1.3
1969 (1)	26	2.23 ± 0.14	35.4 ± 1.9	18.9 ± 1.0
(2)	23	2.55 ± 0.18	38.0 ± 2.2	20.2 ± 1.2
(3)	28	2.25 ± 0.13	36.2 ± 1.8	19.1 ± 1.0
(4)	34	3.05 ± 0.24	41.5 ± 1.5	21.5 ± 2.5
1970 (1)	31	2.79 ± 0.19	39.9 ± 2.4	20.8 ± 1.0
(2)	15	2.50 ± 0.11	37.0 ± 1.7	19.6 ± 0.8
(3)	14	2.35 ± 0.12	36.7 ± 1.7	19.1 ± 0.7
(4)	38	3.07 ± 0.17	43.6 ± 2.0	23.2 ± 1.0

Table 1b Concentration of ^{137}Cs in Females. Mean Values for Quarter-Year Periods (with s.e.).

Year	No.	Total nCi	pCi/kg body wt.	pCi/g potassium
1967 (1)	47	4.67±0.33	84.2±6.5	49.2±2.6
(2)	41	3.99±0.28	67.0±4.4	45.0±3.3
(3)	67	3.33±0.10	58.4±2.1	38.8±1.1
(4)	28	3.09±0.15	54.9±3.9	36.1±1.8
1968 (1)	53	2.34±0.08	38.4±1.4	25.8±1.0
(2)	65	2.09±0.08	34.3±1.2	24.0±0.9
(3)	65	2.11±0.07	35.4±1.0	25.1±0.8
(4)	57	2.23±0.09	35.9±1.4	25.4±1.0
1969 (1)	31	1.68±0.08	28.9±1.2	18.3±0.8
(2)	24	1.71±0.11	30.9±2.8	17.6±1.0
(3)	19	1.68±0.14	33.5±1.6	21.8±1.7
(4)	29	1.87±0.09	33.6±1.7	21.9±1.1
1970 (1)	16	1.79±0.13	30.1±2.0	20.3±1.1
(2)	10	1.67±0.16	30.4±1.9	20.3±1.3
(3)	11	1.57±0.13	30.0±1.9	18.5±1.0
(4)	20	1.60±0.16	31.9±3.0	19.9±2.0

found to be 75 and 39 litres of milk per quarter year. The half-life value for men agrees very closely with 134 days reported for the slow turnover compartment⁵ determined by retention of a single administration over a period greater than five hundred days. The agreement indicates that the assumptions underlying the model are not seriously in error. Lower calculated values of intake for the female population could possibly be due to a combination of two factors; smaller actual dietary intakes, and a larger fraction being rapidly excreted.

It is probably that the former factor is the more important. There are no published data on the relative caesium intakes of men and women, but Harries *et al.*⁹ have reviewed work on energy intake and expenditure. Comparing results for groups of men and women matched according to age and occupation, they show that women have a consistently lower mean calorific intake than men. Therefore, assuming that women have a diet similar in composition to that of men, it is likely that they will also have a lower dietary intake of ^{137}Cs .

We thank Miss D. W. Krupowicz for carrying out the measurements of caesium-137 body burden.

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Avery in Retrospect

Lederberg¹ and Olby² cite enough references to show that many biologists quickly recognized the significance of pneumococcal transformation by DNA. The history of such a subject has great intrinsic interest, and often acts as a cautionary tale that should suggest that there are oversights and false assumptions at the present time. It may therefore be permissible to add something more to the record.

In the spring of 1936, I worked for a few months with Landsteiner in the Rockefeller Institute. Avery often joined us at lunch-time and on several occasions conversation turned to

the possible mechanism of the "Griffith phenomenon" as Landsteiner tended to call it. Landsteiner, undogmatically, tended towards a Darwinian explanation with differential survival of pre-existing bacterial types to which Avery pointed out many objections. At the Microbiological Congress in New York in 1939 I did not see Avery but asked Landsteiner whether any work was being done on the "Griffith phenomenon". He said he thought not.

As Lederberg points out, the paper by Avery, MacLeod and McCarty³ was discussed both in public and private at the 1946 Cold Spring Harbor Symposium and at a Society for Experimental Biology Symposium also held in the summer of 1946⁴. It was the first paper cited by Kalckar. Stacey remarked "There is no doubt that this is an authentic case of a specific mutation caused by a chemical entity, and its importance cannot be over-emphasized". Reference to the work also appeared in a subsection called "Mutation theory of etiology of cancer" in a paper by Stowell. Darlington did not mention Avery but called nucleic acid "the molecular midwife of all reproductive particles". That symposium was also notable because the chemists at it showed that they had at last realized that the tetranucleotide hypothesis was baseless and implausible. A year later, at a symposium in Stockholm⁵, Boivin mentioned Avery's work in a paper with the magnificent title "Le rôle des deux acides nucléiques dans la constitution et dans la vie de la cellule bactérienne, et plus généralement de toutes les cellules vivantes". In 1949 a Society for General Microbiology Symposium⁶ was enlivened by intermittent discord between Harriett Taylor, who was working in Avery's laboratory, and Stacey. They disagreed profoundly on the interpretation of the work but agreed completely about its importance. The editors reported that discussion tactfully.

All those working on viruses, who were reasonably well informed, knew of the suggestion by Muller⁷ and Duggar and Armstrong⁸ that there were many analogies between viruses, and genes that had broken loose from their moorings. The suggestion is quoted in many papers published in the 1930s, and we followed with interest any genetical, or quasi-genetical, research that seemed relevant. It is not surprising therefore that Stanley and Knight⁹, who were at that time on the staff of the Rockefeller Institute, referred to Avery's work in a review in 1945. I referred to it in a review in 1948¹⁰ and Bawden in the third edition of *Plant Viruses and Virus Diseases* in 1950¹¹.

Bearing in mind that scientific communication and publication did not get properly restarted until 1947, and that scientists have never responded quickly to a change in fashionable assumption as great as that involved in the dethronement of protein and polysaccharide by nucleic acid¹², I feel that Avery's explanation of the "Griffith phenomenon" was incorporated into the general picture about as quickly as could have been expected.

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BOOK REVIEWS

In Honour of J. L. Synge

General Relativity. Edited by L. O'Riada. Papers in honour of J. L. Synge. Pp. ix + 277. (Clarendon: Oxford; Oxford University: London, August 1972.) £7.

DURING his long illustrious career J. L. Synge has held mathematical posts of the highest distinction and influence in Ireland, Canada and the United States. The mathematicians who in one way or another stand in his debt could have produced a mighty library of volumes in his honour on his recent 75th birthday. As it is L. O'Riada and the other editors of the present book have selected general relativity as the field with which the name of Synge is most indissolubly linked. Within that field they have selected certain topics upon which they have contributions by Lanczos, Balazs, Ellis and Sciamia, Ehlers and Pirani and Schild, Trautman, Penrose, Bonnor and Vaidya, Taub, I. and J. R. Robinson, Florides, Chandrasekhar, Israel, Thompson. The outcome is a balanced, high grade, contemporary conspectus of typical work by leading workers, which should prove of greater lasting value than most such compilations.

The first section, "General reviews", ranges from history to a rather global survey of "Global and non-global problems in cosmology." The second is called "Mathematical foundations"; it deals with some deep problems of the formulation of general relativity and is the most sophisticated part of the book. The third section is about "Solutions to Einstein's equations" concerning the accelerated charged particle, self-gravitating fluids, the general motion of a massive particle in general relativity, rotating bodies. The last section, labelled "Thermodynamics", deals with the relativistic equilibrium of a certain model "star", the relativistic Boltzmann equation, and the relativistic kinetic theory.

The book has the air of lively, high-level, intellectual activity. In the nature of the case, it deals with the understanding of relativity theory more than understanding the physical world. But, after all, much of the mathematical work of the two centuries following Newton dealt with abstract analytical dynamics and not with real physics; yet in due course some of the most abstract (Hamiltonian) theory proved to be exactly what was needed as a starting point for quantum mechanics in dealing

decidedly with real physics. Some of the developments described in this book may likewise find unexpected applications. Indeed, there are astrophysicists who believe that this is already happening in regard to gravitational collapse, gravitational radiation, and the like.

The way Synge himself features in the work is shown—inadvertently—by the frontispiece. This is a picture of his well filled blackboard, with Synge in the middle distance, in characteristic pose all right, but not quite in focus. The introduction is a brief appreciation, and at the end of the book there is a laconic *curriculum vitae* followed by a bibliography of eleven books and over 200 "other publications", some "in press", showing how active Synge remains. The want of more personal prominence is consonant with Synge's lack of self-seeking. Nevertheless, he is one of the most powerful and colourful scientific personalities of his time; while this book does due honour to his scientific standing, one hopes very ardently for another in which the blackboard will change places with the man.

W. H. MCCREA

Science of Surfaces

Progress in Surface Science. Edited by Sydney G. Davison. Vol. 1. Pp. xii + 420. (Pergamon: Oxford and New York, June 1972.) £12.

SURFACE scientists, on the whole, have very wide interests, as instance the founding fathers Hardy, Langmuir and Rideal. Traditionally a field for physical chemists, there is increasing participation by physicists and biologists. This makes the topic educationally broad, particularly valuable therefore for postgraduate students. The present series starts off on sound lines with articles by Goodwin and Mark on the "Influence of Chemisorption on the Electrical Conductivity of Thin Semiconductors", and by Wociejowski on the "Quantum Theory of Adsorption on Metal Surfaces". There follows S. R. Morrison's "Surface Phenomena associated with the Semiconductor/Electrolyte Interface" which deals clearly with an area of interest to electrochemists. Morrison's contribution raises the problems involved in marrying the electronic energy bands to the ionic double layer at the interface. T. W. Haas and four colleagues contribute a "Bibliography of Low Energy Electron Diffraction and Auger Electron Spectroscopy", a somewhat

odd idea which, on reflexion, has a certain utility. But if all the articles had this character (of bibliographies), I doubt whether the series would attract many readers. An article by N. I. Ionov deals with "Surface Ionization and its Applications", a clear account of the theoretical background of a subject linking up with a number of important practical applications (mass spectrometer ion sources is one). Finally, Weiss and Harlos, in "Short-Term Interactions between Cell Surfaces", start from DLVO theory and end with experiments on cell adhesion, but omit considerations of specificity. The Wociejowski and Ionov articles have been adapted from previous publications in Polish and Russian respectively.

On the whole, the volume is of great interest and one can state that a good start has been made with the series. In name, however, it differs by only one word from *Recent Progress in Surface Science*, which is already established in the literature. Some confusion is clearly possible here unless the full references, including publishers' and editors' names, are cited (as they usually are). *Recent Progress* so far seems to have laid weight on the colloid side, while *Progress* in its first volume emphasizes the physics side. The danger of two review journals for one topic lies in the possible lowering of standards and duplication of effort. This problem arose in catalysis some years ago, however, and the indications there are that the material available is sufficient for standards of both these publications to remain high and one must confidently expect that the same will prove true for surface science.

D. D. ELEY

Photosynthetic Enzymes

Photosynthesis, Part A. Edited by Anthony San Pietro. (Methods in Enzymology, Vol. 23.) Pp. xix + 734. (Academic: New York and London, August 1971.) \$29.50; £13.75.

WHAT does the laboratory worker do if he wishes to prepare or assay an enzyme? If he is lucky enough to work in some institutions he may need do no more than walk down the corridor and ask the expert. In other circumstances he may go to the *cordon bleu* of enzymology as represented by the volumes in this well known series. The rationale is much the same as in *haute cuisine* and a good recipe clearly deserves a better fate than to perish

overnight. Beyond this it is perhaps at first a little surprising that the rate of innovation in biochemistry does not make these expensive volumes obsolete as fast as they are produced. Even I, who in more optimistic moments would barely admit to incipient middle age, can recall (with the pride usually reserved for those who have served their time in sail) that as a research student I was once expected to prepare not only the enzyme but also the coenzyme and the substrate for an assay which must have now been available in the Sigma catalogue for all of fifteen years.

Why is it, then, that "Methods" continues to go from strength to strength? Partly because the rate of innovation is really less rapid than it may seem to those of us struggling to keep pace and partly because the series itself has widened its scope. Thus, while it may now be commonplace to buy ATP off the shelf, P700 is still something for the year 2001. By and large, volume 23 is concerned with things of this sort which will not become commercially available in the immediate or even in the foreseeable future. In addition, like its predecessors in the series, it carries a wealth of factual information about enzyme characteristics and so on, much of which will hardly date at all. Moreover, there is a considerable convenience value in the collation of so much relevant knowledge and I can imagine no one in the field of photosynthesis who would not be glad to see this book on his laboratory shelves or in his department's library. I would have added that each of the sixty-nine articles is written by an undisputed authority. Unfortunately, having contributed an article myself, my difficulty is apparent because if I suggest that (in this one respect) his judgment erred, I impugn the skill of an editor (Anthony San Pietro) whose choice, I must confess, I greatly admire. Certainly most of the authors are workers whose names have come to be associated with the topic of their contribution and, while it would be idle to suppose that many of the articles could not have been written equally well by others, who would deny the aptness (to give only one out of a long list of equally appropriate examples) of "Plastocyanin" by Sakae Kato?

The volume is divided into four sections. The first is concerned with "Isolation and Culture Techniques" (including enrichment, isolation of photosynthetic bacteria and algae, synchronous culture, tissue culture). The second is headed "Preparation and Properties of Mutants" and deals with these topics in relation to *Chlamydomonas*, *Scenedesmus*, *Euglena*, *Chlorella* and tobacco. Section III is devoted to "Cellular and Subcellular Preparations" (cells, chloroplasts, chloroplast frag-

ments, chromatophores and chromatophore fragments). Section IV, much more heterogeneous and simply labelled "Components", includes thirty-seven very valuable contributions ranging through organelles (such as peroxisomes), enzymes (for example, ribulose diphosphate carboxylase) to "Photochemical Reaction Centres".

D. A. WALKER

Investigating Alcohol

Actions of Alcohol. Vol. 1: *Biochemical, Physiological and Psychological Aspects*. Pp. xiv+1-400. Vol. 2: *Chronic and Clinical Aspects*. Pp. viii+401-871. By Henrik Wallgren and Herbert Barry III. (Elsevier: Amsterdam, London and New York, 1970.) £24.

THERE has been a plethora of accounts during the past year devoted to a general review of the biology and actions of alcohol. Of these accounts, the two volumes on the actions of alcohol by Wallgren and Barry provide the most readable and integrated description of the subject. The two authors, one of whom received his initial training in physiology and the other of whom is a sociologist and psychologist, worked together over a seven-year period to produce this comprehensive account of the biochemical, physiological and psychological aspects of alcohol in the first volume, and about its chronic and clinical aspects in the second volume. The authors have carried out a thorough survey of the references on their subject since 1940. Sixty-three per cent of the 3,192 references quoted are to articles appearing between 1961 and 1970.

A short description of the main points in the references is given in individual chapters. The subject matter is well organized so that information about individual subjects is collected together. However, very little comment is made about the implications of the subject matter in the body of the text. Discussion is confined mainly to the chapter summaries and to the final chapter of the book. The text is easy to read and contains few errors.

Each chapter contains references to material in other chapters. This enhances the value of the whole account in that it emphasizes, and shows the connexion between, the diverse points often covered in single scientific papers, and relates them to the whole subject. This integrative aspect is particularly manifest in the chapter on the action of ethanol on the nervous system in which the cellular basis of its action is discussed in relation to its effect on membrane permeability, its effect on active transport and interference with the excitation cycle. The other example of a useful

summary is provided in the table correlating the joint actions of acutely administered ethanol with other drugs. This table is subdivided by classes of drugs. Under each drug the species on which the observation was made is listed, the type of observation is described and the type of combined drug action is specified pharmacologically. This most valuable table is further expanded by descriptions of how drugs may modify absorption and penetration of ethanol in the alimentary canal and other tissues, and how they may alter its metabolism or excretion.

Specific criticism can be made of sections of the book. For example a short account is given of the determination of alcohol on body fluids and tissues in which reference is made to the shortcomings of some methods including breath analysis. It would have improved the text and helped the reader considerably if a table showing comparative values obtained by the different methods had been included. In the description of studies in which the consumption of different concentrations of alcohol by rats is discussed, it is stated that a single alcohol concentration may suffice for comparing different strains or other experimentally varied conditions. This statement is not acceptable by all workers in the field. Unfortunately the references in *Science*, in which this matter is fully discussed, are not quoted. In the discussion of aversive methods for the treatment of alcoholism, the authors suggest that disulfiram may act through an aversive effect, although elsewhere they describe the biochemical mechanism which arrests the onset of ethanol metabolism at the stage of acetaldehyde. However, they state that the toxic side-effects which arise from raised blood-acetaldehyde levels can hardly explain all the symptoms in the alcohol-disulfiram reaction. They compare this type of therapy with the therapeutic production of counter conditioning with electric shock of which they give only a short account. The two types of therapy seem hardly comparable and it is unfortunate that they do not give a full account of the procedures involved in electric shock therapy. They do point out that both types of therapy have the common factor of counteracting only the symptom of excessive drinking without directly affecting the motivations which induce drinking. This seems unsubstantiated for the cases in which the therapy is effective. In discussing the desirability for abstinence in the treated alcoholic the authors point out the problems which face the clinical scientist in designing trials to find out whether moderate drinking is possible in recovered alcoholics. However, they rightly indicate that the ultimate goal of research on therapy should be the

development of methods which enable controlled drinking rather than permanent abstinence.

As stated in the preface, these two volumes should be an indispensable desk companion for all scientists engaged in research on alcohol. The sections on therapy of alcoholism and on alcohol programmes are not so comprehensive as the experimental physiological, biochemical, and pharmacological sections, though they will be of value to therapists and educators for reference. The two volumes are expensive for an individual or a department to purchase, but when they are purchased they will be found to be of great assistance in the design of investigations on all aspects of the actions of alcohol.

C. W. M. WILSON

Traditional Topology

Fundamental Concepts of Topology. By Peter V. O'Neil. Pp. xv+320. (Gordon and Breach: London, May 1972.) £8.10.

THIS book covers a more or less traditional account of general topology from its beginnings in the axioms for open sets to compactness, the Baire category theorem, and an introduction to topological groups. The amount of material contained is indicated by the fact that sufficient is developed to be able to sketch the existence of Haar measure on topological groups. The book also has a brief introduction to homotopy and the fundamental group.

The care taken in the exposition is indicated by the fact that topological spaces are always denoted by pairs such as (X, T) where T is a topology on X . For extra clarity, the theorems and definitions are printed so that each main clause has a separate line, as in

Let $B \supset A$.

Then,

B is T_A -closed

if and only if

for some F , F is T -closed and $B = A \cap F$.

One useful feature is the emphasis placed throughout on the construction of examples and counter examples. There are also useful diagrams of implications among many of the topological properties.

I noticed one error, namely, the statement of 11.5.5: in fact, homotopic maps need not induce the same homomorphism of fundamental groups unless the homotopy is relative to the base point.

Finally, in spite of the book's potential usefulness, I think that it will find very little following for students in this country because of its price, which is in excess of that of a number of competing books.

R. BROWN

Enzyme Principles

Enzymes: Physical Principles. By H. Gutfreund. Pp. xii+242. (Wiley: New York and London, April 1972.) £5.50.

THE author starts by declaring that his "main prejudice is that an understanding of physical principles is more important than the memorizing of facts". A tragedy of much of today's scientific education is that although both pupil and teacher are committed to this "prejudice", neither recognizes the other's commitment. The book's contribution here is excellent; the author continually points out the relevance of his treatments, and he accompanies them with beautifully chosen examples and applications and with wise comment.

The core of the book is its treatment of ligand binding and of steady-state and transient kinetics. This part is excellent, and it follows a helpful introduction on chemical equilibria and reactivity in aqueous solution.

Unfortunately the formal treatments are often obscure. The author's aim of giving only outlines so that readers can learn by filling in the details sometimes succeeds, but frequently the omission of information essential to understanding the argument, or vague description (for example "the energy expended to keep two particles at a distance r "), mars the treatment. There are also several small errors, which are particularly unfortunate for the student who meets the treatment for the first time. Nevertheless those actually concerned with enzymes have much to learn from the book and they will find it exciting. Some concepts, such as the Hill coefficient, are particularly well explained. The pertinent examples, although not always followed up enough, encourage readers to return to topics and read around them. This is made easier by the manageable size of the reference list.

It is a pity that the curve showing the Michael relationship is grossly distorted; the ratio of the rate to the maximum rate is shown as 0.7 instead of 0.5 when the substrate concentration is equal to the Michaelis constant, and as 1.0 instead of 0.75 when the concentration is three times this. More serious errors are rare. One is that steady-state kinetics are said to provide information about the intermediate immediately before the rate-determining step (when there is such a step). In fact, however, if one step is rate determining, all intermediates before it will be in equilibrium, and information (on pK values, and so on) refers to a weighted average of all of them; if one such intermediate greatly predominates, the data refer to it. Another passage that could mislead concerns the Brönsted coefficient β , for low values are said to indicate general-base rather than nucleophilic character for the catalysis. The

value of β may indicate the extent of bond formation in the transition state; it is true that nucleophilic catalysis usually involves reaction of the nucleophile before the rate-determining step, and hence complete bond formation and high β values, but the nucleophilic attack could itself be rate determining and the catalysis could thus exhibit a low value for β .

Such faults are rare and the book clearly brings out the varied physical approaches to enzymes and how they complement each other. Those concerned with enzymes should read it; the stage at which they will find it most helpful may be when they already know a fair part of its contents, and then they will be keen to re-read some parts quite often.

H. B. F. DIXON

Coffee Table Hale

The Legacy of George Ellery Hale: Evolution of Astronomy and Scientific Institutions in Pictures and Documents. Edited by Helen Wright, Joan N. Warnow and Charles Weiner. Pp. 293. (MIT: Cambridge, Massachusetts, and London, 1972.) \$17.50.

FROM any standpoint George Ellery Hale was a remarkable man. He became a pioneer of big science and one of the ablest grant-getters and organizers of science ever seen. Apart from his endeavours on behalf of astronomy, he stimulated the development of the California Institute of Technology towards its present eminence, obtained the endowment for the Huntington Library and Art Gallery, and created the National Research Council. Yet, when he was forced by ill-health and nervous breakdowns to resign the directorship of the Mount Wilson Observatory, he returned with undiminished enthusiasm to his own private observatory and to his first scientific love—the observation of solar phenomena.

Hale's career clearly demands close attention from historians of science, for it raises some important questions. To what extent can the current American domination of observational optical astronomy be attributed to his influence? More generally, did his success in obtaining grants for scientific research have any effect on the subsequent growth of big science in the USA?

There is therefore good reason why the publication of additional material on Hale's activities should be welcomed. Unfortunately, however, the present volume does not really live up to the promise of its title. What it provides is rather a kind of *Festschrift* in three parts. The first, a brief biographical account of Hale by Helen Wright, although thoroughly acceptable, hardly adds to the full-length biography she has already published. Five of Hale's

numerous writings have been selected for reprinting in the second section, the most interesting certainly being the text of the physics thesis he submitted for his bachelor's degree at MIT in 1890. This thesis, devoted to the photography of solar prominences, effectively foretold the main research interest of his life. The final section contains four articles mainly concerned with tracing the development of certain areas of scientific interest to Hale from his own lifetime to the present day. They provide quite useful summaries, but are too brief to allow of treatment in any depth. Moreover, a slight up-dating of some of the contents might have been advisable, since the material in this part of the book was originally presented at a Hale Centennial Symposium in 1968.

The book really must be judged, however, less by its text than by its illustrations. In one sense, indeed, this is a book for the coffee table: the format is large, the layout lavish, and the visual material extensive and attractive. But historians of science have, perhaps, laid too little emphasis on the visual aspects of their subject. It is only fair, therefore, to welcome the quite different stress of this new volume and the additional material on Hale that it provides.

A. J. MEADOWS

Mighty Whale

The Whale, Mighty Monarch of the Sea. By Jacques-Yves Cousteau and Philippe Diolè. Translated from the French by J. F. Bernard. Pp. 304. (Cassell: London, September 1972.) £2.75.

DURING a recent visit to the Smithsonian Museum of Natural History in Washington I expressed to a colleague my admiration for the full-scale model of a blue whale suspended from the ceiling in one of the Museum's galleries, and commented on its similarity to one I had seen only the day before in the New York Natural History Museum. My friend offered the explanation. The resemblance was not accidental, for the New York Museum authorities had borrowed the original mould for the model from the Smithsonian, but to make things a little different they had added an extra foot or so to their whale to lengthen it.

I mention this story because it is indicative of the obsession mankind, even museum curators, has with "bigness", from extra large packets of washing powder to Everest and the Empire State Building. This infatuation with bigness has enabled the whales, and particularly the blue whale, to attract the attention and unfailing admiration of humans. The fascination in whales for man goes back to prehistoric times as is attested by rock and cave paintings; and they have been the subject of

writers from the Bible onwards. The great sperm whale fishery of the 18th and 19th centuries for example provided a wealth of material for literature and spouted Melville's classic *Moby Dick*, but recently because of the increase in our knowledge of whales and our concern for their diminishing populations books have been coming off the presses in ever-increasing numbers. And so it is not surprising that Jacques-Yves Cousteau has wanted to add his contribution. From him we should have expected a book at least on a par with his *The Silent World*—alas, *The Whale, Mighty Monarch of the Sea* comes nowhere near that earlier book either in style or content. At best we can say that there are some useful observations and just occasionally the Cousteau magic shows through, but the author fails to hold the reader's attention and much of the text is not worthy of his talents.

But whatever it lacks in the way of text it more than makes up for this in the illustrations. This volume is a treasure-house of unique and spectacular photographs of whales at the surface of the sea and in it, a collection of pictures which would have been worth publishing on its own. Others may have dived alongside finners and hump-backs but none have brought back gems such as are presented here.

In the past much of our knowledge of whales has been learned from the "bloody" dissections on the decks of factory ships and land stations and perhaps more recently our knowledge of their behaviour has been enhanced by observations in oceanaria. Even so, many questions about these animals remain to be answered, for example, how do whales behave and appear underwater in the open ocean? The Cousteau photographs will be invaluable in this respect for the student of cetacea, while for the layman they can only add to his fascination for these magnificent marine mammals of whose "bigness" he is already aware, but when he sees the picture of a diver alongside one of them he will realize their true dimensions.

There are some minor irritations; one or two of the captions are misleading and the *Calypso* crew demonstrate a little too often how photogenic they are. *The Whale, Mighty Monarch of the Sea* is one of a series being published by Cassell under the general title *The Undersea Discoveries of Jacques-Yves Cousteau*, and I cannot help feeling that the author, or the publisher, has been in too much of a hurry to get this book, and the one that preceded it, into print. One can only hope that in the future Cousteau will be able to give more time to writing the text and produce a volume which will do him justice and perhaps emulate the quality of *The Silent World*. ARTHUR BOURNE

Sediment on the Move

Mechanics of Sediment Transport. By M. S. Yalin. Pp. xii+290. (Pergamon: Oxford and New York, July 1972.) £9.

ALTHOUGH it is intended to give graduate students and research workers a guide to the extensive literature, this treatise is most notable for the proportion of hitherto unpublished analyses, interpretations and hypotheses, and of suggestions for future research programmes. One must therefore infer that the author's primary concern has been to attempt a dominating, and somewhat pre-emptive, guide to research, which may, in the future, be considered to have established significant trends. Only in the future will it be possible to assess the degree of success, but all research workers in sediment transport and related matters should find great interest and considerable value in the work.

After three introductory chapters, the remaining five chapters treat differing aspects of idealized sediment transport; initiation, rate, suspended load, sand waves and friction. Intentionally, but regrettably, there is little attempt to relate the new work contained in the treatise to practical situations, although river data are quoted. The author's background makes his complete avoidance of régime theory the more strange. It is in the generalization of the latter approach and its integration with the theory of idealized sediment transport, and with the findings from controlled experiment, that there is the greatest potential for advances of immediate significance in river mechanics.

Recurring throughout the book is the question of characteristic Shields diagram dip, and of its relationship with the Nikuradse uniform sand roughness form of transition. Now that the Nikuradse transition has been evaluated numerically, with a plausible physical argument for the form of transition control function, corresponding advances may be expected in the generalization of the Shields diagram and of similar findings.

I recommend a careful study of the work to all active research workers. It could also be of value in graduate studies but in conjunction with one, or both, of the other comprehensive English language texts which have been published within the last year or so.

D. I. H. BARR

Erratum

IN *Nature* (240, 243; 1972) the price of the book, *Living on the Third Planet*, by H. Alfvén and K. Alfvén, was given as \$29. The correct price is £2.20.

CORRESPONDENCE

Creation in California

SIR,—Your attitude to California's creationists is understandable. Unfortunately, it will help to perpetuate two popular fallacies which call for correction.

First, not all Bible-believers are like those referred to in the Californian textbook, who seem to think the Earth was created in six literal days, only a few thousand years ago. Such fundamentalists are right at one end of a long spectrum of belief. Others—probably a much larger number—accept the facts of geology, but think that the idea of many successive creative acts over the ages fits those facts better than the theory of natural evolution. Further along the spectrum still are a great number of theistic evolutionists, who think that some kind of evolution did occur but that natural selection alone cannot account for it: according to them, a liberal application of divine creative power must have been needed to make evolution work.

Secondly, there are more anti-Darwinists in British universities than you seem to realize. Among them is a friend of mine who holds a chair in a department of pure science "in a field bearing on the evolutionary question", to use your phrase. If his friends ask why he keeps quiet about his unorthodox views, he replies in words very like those used recently in another connexion by Professor Ian Roxburgh:

"Science is only concerned with the truth, and as the way to truth is by conjecture and refutation, why don't they (orthodox scientists) listen? Science is not like that at all. There is a powerful establishment and a belief system. There are power seekers and career men, and if someone challenges the establishment he should not expect a sympathetic hearing."¹

The majority of biologists accept the prevailing views uncritically—just as a great many competent Russian biologists were once brainwashed into accepting Lysenko's quackery. Others have thought for themselves and come to realize the flaws in contemporary Darwinism. But for them to speak out would be to invite ridicule, and probably ruin their careers. Can you blame them for keeping silent? Do you really suppose that the offer of a year's free subscription to *Nature* will tempt them to expose themselves?

Only a man at the peak of his career could afford to do this, as W. R. Thompson once did. Shortly before he retired he was invited to write an intro-

duction to a centenary edition of *The Origin of Species*. This eminent entomologist, whose recent obituary in *Nature* described his career as "long and distinguished" and his impact as likely to be "of lasting academic value"², declined because he was no Darwinist. Eventually he was persuaded, and wrote a highly critical introduction in which he said:

"It does occur to me, in the first place, that Darwin in the *Origin* was not able to produce palaeontological evidence sufficient to prove his views, but that the evidence he did produce was adverse to them; and I may note that the position is not notably different today.

"... This situation, where scientific men rally to the defence of a doctrine they are unable to define scientifically, much less demonstrate with scientific rigour, attempting to maintain its credit with the public by the suppression of criticism and the elimination of difficulties, is abnormal and undesirable in science. Thus are engendered those fragile towers of hypotheses based on hypotheses, where fact and fiction mingle in an inextricable confusion."³

These are not isolated remarks taken out of context. They truly represent Thompson's views. Anyone who thinks that only uninformed cranks reject Darwinism should read the whole of Thompson's *Introduction*. It will make him think again.

Yours faithfully,

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¹ *New Scientist*, September 28, 602 (1972).

² *Nature*, 238, 116 (1972).

³ *Everyman Library* No. 811 (Dent, London, 1956).

Objective Testing

SIR,—May I answer Roy Cox (*Nature*, 237, 189; 1972) on the advantages claimed for objective testing (OT) over the "essay" paper? I must stress that the so-called "essay" paper usually has some questions to which essay answers are necessary and also fragmented questions ("Write notes on: . . .", and so on) and often one or more problems.

After quarrelling with Dr Cox over several specific points, I should like then to deal with other points he did not mention.

(1) In the older type of OT, the

answer is a word or phrase. Since there are no suggested answers to prompt the candidate, we may call this type "recall" OT (ROT). In the modern multiple choice or matching, the answer is suggested—"suggestive" OT (SOT). When it is desirable to expect a candidate to know not an exact answer but merely a range in which the answer may be, SOT can be useful, for example, that the Battle of Hastings was in 1066 rather than 55 BC, 1492, 1815 or 1942. But this is the kind of SOT question for which it is most difficult to obtain other equally plausible suggested answers, or "distractors". In most cases, however, it seems to be used in preference to ROT either to allow mechanical marking or merely to be fashionable.

(2) The student can know what to expect just as easily in a well set essay paper as in an OT paper. How is a reappraisal of study objectives prompted more effectively by OT testing?

(3) The National Board of Medical Examiners compared OT and essay marks with something even more subjective than the latter—teacher opinion. Such a comparison is worthless.

In the work cited of Anderson, Dykes and Lennon, OT and essay marks were compared with the totals of both. Unfortunately, any unreliability in *X* or *Y* must be reflected in *X* + *Y*.

Two important advantages of OT are readier obtaining of spread and accuracy of marking.

(1) To be fair, a paper must cover the syllabus as widely and as evenly as possible. Although easier with a 50- or a 100-question OT paper than with a 6- or 8-question essay paper, spread can be obtained in a carefully set essay paper—and an OT examiner can allow his enthusiasm for certain areas of work to lead to bad spread.

(2) The more subjective the answers, the more difficult the marking. Essays are necessarily more subjective than answers to fragmented questions or problems, and, of course, OT questions. But difficulties with essay papers are often exaggerated and can largely be overcome. Because of the number of questions in an essay paper and of papers in an examination, errors in the marking of essay questions will tend to cancel one another and the residual cumulative error is buffered by the greater accuracy in marking fragmented and problem questions. Use of a marking scheme can sharpen accuracy of marking and increase agreement among those marking the same material. The more specific the wording of the ques-

tion, the less room there is for differences of opinion on what is wanted in the answer. Finally, I must stress that, although in OT ranking order is exact, there is still the question of where to put both the pass-fail and any inter-class barriers.

Certain disadvantages of OT should be mentioned.

(1) Setting can be as time-consuming as machine-marking is simple. Spread must continuously be checked; the position of the right answer must be varied; distractors must be both plausible and of similar plausibility. Finally, in the marking, there must be a penalty for guessing.

(2) Especially in SOT, there is only one right answer. Especially in science, a particular point may be very debatable and anything but simple. Like programmed learning (get the sole accepted answer before going on to the next step), OT can inject an unhealthy authoritarianism and superficiality.

(3) In general, both knowledge of facts and ability to apply them should be tested. Ability to choose relevant facts and marshal them in logical order can be tested only by the essay (or orally). Even if there is a problem in an OT paper, one can know only what answer has been derived (or, in SOT, selected). What is much more important, how this was deduced can never be known.

(4) At times OT can test even factual knowledge only in a very cumbersome manner if at all. The sensible test of a definition is to ask for it—which may be beyond the scope of an ROT question; ability to translate (knowledge of vocabulary and grammar) can be tested only by translation; knowledge of phonetics is best tested by writing a passage in phonetics; one of the best tests of familiarity with literature is the question "Assign to context: . . .".

(5) Such a question as "With an example for each consonant mentioned, give an account of Grimm's Law", although an essay question is not only about the only one that could be asked on the Law, but is also quite objective. All these examples are of areas in which the "essay" question is superior to the OT question in testing factual knowledge and can be marked as accurately as the latter.

OT is not to be condemned bell, book and candle. All methods of examining have their merits and demerits. Since Dr Cox's paper leaned heavily towards OT, it is only right that my reply should emphasize the opposite case.

Yours faithfully,

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Cancer Research

SIR,—Dr John Paul comments (*Nature*, 240, 492; 1972) on your correspondent's report entitled "Lord Zuckerman Defends his Position" (*Nature*, 240, 247; 1972) and refers to what I said at the meeting of the British Association for Cancer Research.

I spoke about the development of the four new oncological centres, made a plea for closer integration of work being done in laboratories, in clinics and in the field and asked for greater emphasis on the flow of ideas from clinic to laboratory. I also asked some questions about accountability, effectiveness and efficiency, suggesting that in the context of the human cancer problem it was no less necessary and no more invidious to ask for assessment of the relevance and value of work done at subcellular level than it was at patient or community levels.

Dr Paul complains that in advocating greater emphasis on clinically oriented research, I was wrong in claiming that supracellular biologists had made a greater contribution to the welfare of the cancer patient than molecular biologists. The passage from my talk referred to was as follows:

"The mere asking of such controversial questions has been taken by some subcellular biologists to be a denial of the importance of their work, rather than an encouragement of the work of the supracellular biologists who have to date made a far greater contribution to the welfare of the cancer patient. 'Fundamental cancer research' has yet to match the long record of success of clinical and epidemiological investigations to which we owe so much in cancer prevention, detection and treatment. Hormone control of cancer arose from the observations of a surgeon, and both radiotherapy and chemotherapy had their origins in observations of their effects on man. Each clinical discovery has led to the creation of new research departments to fill important feedback functions. Successful preventive measures have stemmed in the case of mouth cancer from the work of the dental profession, and in lung cancer from that of the epidemiologists and statisticians. If cancer research is to advance more quickly toward practical control of the human disease processes involved, rather than make progress in some other if perhaps equally important function, then those engaged must have a close contact with the clinical scene and derive inspiration from it."

Of course it is Dr Paul who is wrong. His suggestion that cancer chemotherapy stemmed from molecular biology is quite untenable; it stemmed from clinical observation, its increasingly effective combinations developed

from clinical practice and biochemistry was brought in later and most helpfully to support, to develop and to attempt to account for the success achieved.

Arguments about the merits of research at different biological levels are unprofitable since we need to understand the mechanisms of disordered growth at all levels of organization. I was discussing emphasis and relative effort. I am glad to see that Dr Paul, though regarding me as "puckish" when I am serious, also regards me as "reasonable" in holding the view that distinctions based on the value of work at different biological levels are pointless and that coordination of work at all levels is essential.

Yours faithfully,

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Acupuncture

SIR,—There has been much recent interest in acupuncture, but as early as 1823 a treatise on the subject was published in England. In the December issue of *The British Critic*, 668 (1823), an unnamed reviewer discusses three new books. Each seeks to introduce a foreign method of medical treatment, and the only one which the reviewer feels is "deserving of serious consideration" is:

"Art XII. A Treatise on Acupuncture; being a Description of a Surgical Operation originally peculiar to the Japanese and Chinese and by them denominated Zin-King, now introduced into European Practice, with Directions for its Performance, and Cases illustrating its Success. By James Morss Churchill, Member of the Royal College of Surgeons in London. 8vo. 86 pp. 4s. Simpkin and Marshall. 1823."

Churchill's book receives the bulk of critical attention, while the other two, a treatise on Fumigating Baths (from France) and a treatise on Shampooing (from India), receive minimal attention as they are thought to be "of little worth".

In several long passages quoted from Churchill's book, the technique of acupuncture is described, and a whole range of maladies for which it had proved useful are mentioned. Churchill cites in particular two cases in which he himself had successfully performed acupuncture. The first was a woman suffering from rheumatic pain, the other was "William Morgan, a young man in the employment of a timber merchant". The latter had strained

himself lifting heavy timbers, and two consecutive treatments of acupuncture, one by a needle "passed to the depth of an inch on either side of the spine", relieved the pain.

In addition, Churchill was aware that "acupuncture" was practised elsewhere and cites several French doctors as having reported success with acupuncture. Also, a Dr Bretonneau, "physician to the 'Hospital General' of Paris, has made a number of experiments on puppies". These prove that "the Cerebrum, the Cerebellum, the Heart, the Lungs, the Stomach, &c. may be penetrated without occasioning the least pain or inconvenience".

Ranging further afield, Churchill also reports a practice among American Indians in which a number of specially constructed arrows (i.e., for shallow penetration) are shot into the patient who is standing in a river. However, he concludes that this is not acupuncture, a bloodless procedure, but is actually a form of bloodletting.

Churchill also discusses the two kinds of special gold or silver needles which the Japanese used for acupuncture. These were made only by expert artists specially licensed by the Emperor. Depending upon their design, the needles were either twisted into the flesh by hand or were driven in by a special leather-covered hammer.

The unknown reviewer, with tongue-in-cheek, suggests that such medical advances might cure the ills of the literary world. He recommends "regular quarantine fumigation" for Lord Byron and Carlisle, shampooing for Mr Wilberforce and "the secondary Scotch novellists", and acupuncture for Joseph Hume and Henry Brougham.

Evidently, mention of or allusions to acupuncture does not appear in early or mid 19th-century popular writing. Certainly it would have been mentioned had it become at all fashionable. Churchill recommends it (as it is touted by some today) as a cure for many ills. Although a surgeon, he seems to have missed its possible use as an anaesthetic during surgery. One wonders why, if it was indeed so effective, acupuncture was not accepted in England or France and retained by the Japanese?

Yours faithfully,

MAUREEN LIPPERT

ERNEST L. LIPPERT, JUN.

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Anglo-Soviet Exchange

SIR,—Your leader entitled "Anglo-Soviet Science — Hopes Revived" (*Nature*, 239, 482; 1972) expresses the hope that the plans for cooperation in

science and technology between the UK and the USSR will be revitalized following the recent visit of a delegation from the Soviet State Committee for Science and Technology. You contrast the failure to implement article 3 of the 1968 agreement which provides for exchange visits by applied scientists and technologists with the success of the Royal Society/Soviet Academy of Sciences arrangement. May I draw your attention to the Agreement on Relations in the Scientific, Educational and Cultural Fields which, in addition to embracing the Royal Society's Agreement, includes provision for exchanges in science and technology with Academy and non-Academy Institutes and Universities. These are administered by the British Council and represent a substantial inter-movement of scientists, both for short-term "familiarization" visits and for longer-term attachments for postgraduate study and research. Sixty-seven Soviet scientists came to the UK in 1971 (56 in 1970), while seventeen British scientists visited the USSR (twenty-four in 1970). The reason for the apparent imbalance is that younger Soviet scientists are particularly keen to pursue postgraduate studies here, whereas the attraction for British postgraduates is greater in fields other than science. Both countries contribute to the cost of the exchanges which provide an opportunity for scientists in a wide range of disciplines to meet and gain research experience.

Yours faithfully,

W. A. BARR

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Algae and Protozoa

SIR,—A sample survey of the literature on algae and protozoa has confirmed the impression that authors do not always give adequate reference to the strains used in work involving cultures.

The sample used was the 1971 issues of fourteen journals taken at this establishment which publish original work on algae and protozoa. Papers dealing with fossils, larger seaweeds and organisms not so far cultured were excluded.

Minimum adequate reference is considered to be the designation of the culture together with, where appropriate, indication of the source collection, for example, CCAP 211/8d or Göttingen 11/6. A more complete reference would give also the name of the isolator and the date of isolation, but this information is usually available in the list published by the collection.

The survey shows that over three-

quarters (153 out of 204) of the authors used cultures when this was possible. It also shows that well over half of the users (eighty-nine out of 153) gave inadequate or no reference to the cultures used. This is most unsatisfactory, especially when one considers the rigid insistence by authors and editors on proper bibliographic references.

References to specific names and a collection, for example, "*Chlamydomonas globosa* from CCAP" are not satisfactory as there may be now, or in the future, more than one strain fitting that description. Also, taxonomic names are liable to revision while strain designation should be immutable. References such as "*Tetrahymena pyriformis* 'W' Strain" are inadequate without mention of the source. It has recently been shown by isozymal tests that strains of this species from different sources but with the same designation may differ, while differently designated strains may be identical. The cause of this confusion presumably lies in mislabelling and failure to record the origin of stocks used. In one paper there was a serious orthographic error in a strain designation.

Among the advantages of using properly documented strains are (a) that the work can be repeated or compared with other work on the same strain, and (b) that comparison of different strains of a species or of different species of a genus enables the significance of the particular characters to be assessed. Too often one sees a general statement about a species made from evidence derived from only one strain.

Wherever possible, cultures of new taxa or new strains used in important research should be deposited in at least one major collection. It is also of great value to a culture collection to receive reprints of work done with its cultures.

Yours faithfully,

E. A. GEORGE

The Culture Centre of Algae and
Protozoa,
36 Storey's Way,
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Potato Blight Teratogen

SIR,—The most recent and dramatic hypothesis to be pronounced about the aetiology of the neural tube malformations, anencephaly and spina bifida cystica, is that published earlier this year by Renwick (*Brit. J. Prev. Soc. Med.*, 26, 67; 1972), where it is suggested that the damaged or diseased and especially the blight-diseased or even blight-resistant potato is in some way related. Renwick cites the time/space relationship between secular changes in malformation rates and the severity of blight in West Scotland, the

United States and other places, and suggests that 95% or more of all cases might be directly caused by some as yet unidentified alkaloid or antibiotic in the potatoes. Some weight is undoubtedly given to the hypothesis by the preliminary findings of Poswillo and co-workers (*Nature*, **239**, 462; 1972) of skull defects in four of eleven fetuses of marmosets fed on diseased potatoes. However, the time/space relationship between malformation incidence and blight is not close everywhere in the British Isles, central nervous system malformations are found in parts of the world where potatoes are not consumed (Emanuel, *Lancet*, ii, 876; 1972), and the marmoset anomalies do not obviously involve the central nervous system. Also, it would be difficult to see how blight, if it is so potent a teratogen as is suggested, would affect only one of identical twins, as happens often, an obvious objection to that as well as other hypotheses. In any case, it is likely that one is dealing with not a single teratogen malformation but one which is multifactorial.

These objections apart, it is perhaps unfortunate and somewhat worrying that the theory has been given so much publicity in the scientific, medical and other press, often in highly emotional terms with claims of a relationship, even if correct, which is most unlikely to be as direct as has been suggested by Renwick. A climate of opinion is being created in the general public which makes it very difficult to launch a properly randomized and controlled trial of potato avoidance in susceptible women going in for a further pregnancy, who have previously had a child with spina bifida or anencephaly. Such a trial is probably the only way in which

this theory could be tested out quickly in man and could probably be completed in less than two years if carried out on a multicentre basis. What is even more worrying is that in the meanwhile some women who have avoided pregnancy for fear of a recurrence might embark upon a pregnancy in the belief that potato avoidance will eliminate that risk.

Yours faithfully,

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Announcements

Miscellaneous

Royal medals of the Royal Society have been awarded to Sir Derek Barton, Imperial College of Science and Technology, Dr F. H. C. Crick, MRC, and Dr W. B. Lewis, Atomic Energy of Canada Limited.

The following have been elected Academicians of the Soviet Academy of Sciences: S. M. Nikol'skii and Yu. V. Prokhorov (mathematics), A. S. Vorovik-Romanov and B. M. Vul (physics and astronomy), A. A. Logunov (nuclear physics), V. S. Semenikhin (information processing), A. D. Sadykov (organic chemistry), A. F. Belov (metallurgy), A. L. Takhtadzhian and D. K. Belyaev (biology). New Corresponding Members of the Academy include: O. B. Lupanov and N. N. Govorun (mathematics), K. A. Valiev, L. N. Kurbatov, Zh. I. Alferov, Yu. A. Osip'yan, I. M. Khalatnikov, V. A. Krat, N. A. Borisevich,

and K. S. Aleksandrov (physics and astronomy), A. M. Baldin, V. N. Gribov and L. M. Barkov (nuclear physics), V. S. Avduyevskii, O. M. Belotserkovskii and V. V. Petrov (control processes), A. N. Nesmeyanov, Kh. M. Minachev and V. P. Mamaev (general and technical chemistry), V. B. Aleskovski and M. M. Shults (physical chemistry and the technology of materials), I. V. Torgov (biochemistry), G. A. Viktorov and A. V. Zhirmunskii (general biology).

Erratum

In the article "Nature of the Molecular Defect in Phenylketonuria and Hyperphenylalaninaemia" by Paul A. Friedman, Seymour Kaufman and Ellen Song Kang (*Nature*, **240**, 157; 1972), the K_m value for DMPH₄ given on line 6 of paragraph 6 should be 0.05 mM.

Reports and Publications

not included in the Monthly Books Supplement

Great Britain and Ireland

University of London. University College Calendar 1972-73. Pp. cvii+303. (London: University College, 1972.) [2310]
The Edinburgh School of Agriculture. Annual Report 1971. Pp. 90. (Edinburgh: The Edinburgh School of Agriculture, 1972.) [2310]
Council for Scientific Policy. Third Report of the Council for Scientific Policy. (Cmd. 5117.) Pp. 35. (London: HMSO, 1972.) 24p net. [2310]
Family Planning in Five Continents. Pp. 34. (London: International Planned Parenthood Federation, 1972.) [2310]
Department of the Environment. Report of Working Party on Local Authority/Private Enterprise Partnership Schemes. Pp. 66. (London: HMSO, 1972.) 47p net. [2410]
Natural Environment Research Council: National Institute of Oceanography. Collected Reprints, Vol. 19. Reprints 778-830. (Wormley, Godalming: National Institute of Oceanography, 1971.) [2410]
Microbiological Research Establishment. Abstracts of Work Published in 1971. Pp. 20. (Porton Down, Salisbury: Microbiological Research Establishment, 1972.) [2510]

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